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PRESENTATION OF KEYES MEDAL TO DR. WILLIAM F. BRAASCH

DR. HERMAN L. KRETSCHMER: Early one morning more than 40 years ago, the telephone rang and a soft spoken voice asked permission to visit the urological department at the Alexian Brothers Hospital. When the young man arrived, he introduced himself as Dr. Braasch of the Mayo Clinic, and said he was interested in urology. From this humble beginning Dr. Braasch has risen to great heights, not only in urology, but in American Medicine as well.

The high esteem in which he is held by his colleagues is shown by the fact that he has been President of the American Urological Association, the American Association of Genito-Urinary Surgeons, and the Clinical Society of Genito-Urinary Surgeons. He is an honorary member of most of the foreign urological associations. In 1937 Dr. Braasch was chosen to deliver the Guiteras Lecture. The only other member of the American Urological Society to be so honored was Dr. Hugh Young. He was asked to give the paper on "A Hundred Years of Progress in Urology" at the Centennial Meeting of the American Medical Association.

Dr. Braasch has taken a very active part in the work of the American Medical Association. Early in his career he served as Secretary, and later Chairman of the Section on Urology. He was among the first urologists to become a member of the House of Delegates, first representing the Section on Urology and then his state. Later he became a member of the Board of Trustees of the American Medical Association and part of this time he served as Chairman of its Executive Committee.

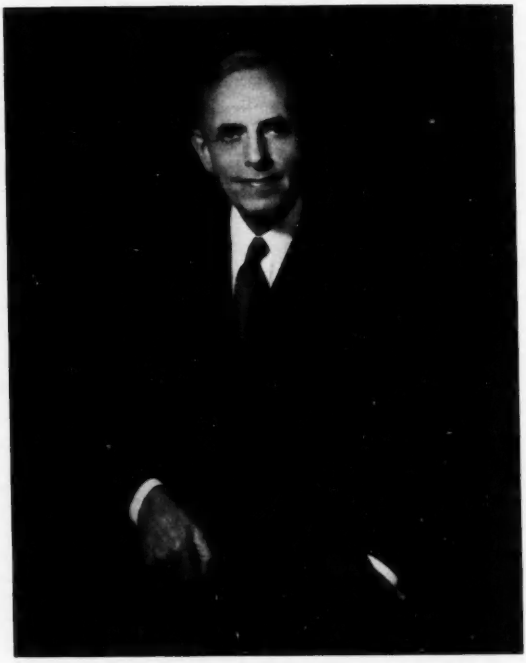
He was also President of the Minnesota State Medical Association which awarded him the Distinguished Service Medal a few years ago. He is now President of the Minnesota Public Health Association. In 1937 Dr. Braasch organized the Northwest Regional Conference. He was instrumental in organizing the National Physicians Committee and served as the Secretary during its entire existence. At the request of the United States Government he with others recently made an extensive survey of the health of the Indians in the Northwest.

Dr. Braasch has always been interested in Medical Education. For many years he was Professor of Urology in the Graduate School of the University of Minnesota. He developed the Section on Urology at the Mayo Clinic and was head of the Section over 35 years. During this time more than 100 Fellows in in the Mayo Foundation were given training in Urology. He served as a member of this Board for eight years. He now is chairman of the Committee on Graduate Education of the American Urological Association which has developed a series of post-graduate seminars held in all parts of the country.

For many years Dr. Braasch was a regular contributor to urological programs. He has enriched our literature with 192 papers covering many fields of urology. These papers drew on the vast clinical and laboratory resources of the Mayo Clinic during the past forty years.

Dr. Braasch was first to describe urographic deformities with such renal lesions

as renal tumor, cysts, tuberculosis, and pyelonephritis. He described urographic identification and localization of renal shadows. He described the inflammatory etiology of certain types of pyelo-ureterectasis and differentiated it histologically and urographically from mechanical causes. He described a form of renal atrophy which he called "Atrophic Pyelonephritis" and was first to outline the urographic deformities which accompany it. He was first to advise fluoroscopy at the operating table with nephrolithotomy. He was one of the first to advise resection of the bladder neck in the presence of spinal cord lesions. In the Guiteras Lecture he described a type of chronic pyelonephritis in which multiple minute stones



are observed in the urogram surrounding the apices of the calyces—a subject of widespread interest today.

Dr. Braasch has been Chairman of the Editorial Committee of the *Journal of Urology*. He has contributed chapters to many assembled books on urology and surgery. He is now a member of the Editorial Committee of *Urological Survey*, of *Excerpta Medica*, and the *General Practice Clinics*. Dr. Braasch was first to publish a monograph on pyelography (1915). His second monograph *Urography*, appeared in 1927, and *Clinical Urography* with Dr. Emmett as co-author was published this year.

Dr. Braasch, in presenting this award to you, I am sure I express the sentiments of the members of this Association when I say that you have served the

cause of American Urology well, not alone by your scientific contributions but by broadening its horizon, by preserving its dignity and by insisting that its standards shall be on the highest level.

RESPONSE BY DR. BRAASCH: As I listen to all this gossip that Herman and Charlie have been telling you, I am reminded of a cousin of ours who is very fond of telling stories on her meek and mild husband, even in his presence. At one time after describing a particularly fantastic episode involving her husband, he said to her "Bertha, was I there?" I might be forgiven for a similar reaction.

Needless to say, I deeply appreciate the honor of receiving the Keyes Memorial Medal. I accept it with some misgiving however, because I realize there are members of this Association who deserve the honor fully as much as I. Brief reference to the man after whom the medal is named would seem most appropriate for this occasion. It is hardly necessary to recall the important contributions to American Urology made by the elder Keyes. He represents the pioneer era of urologic progress and contributed much in a scientific way. Of even greater importance were his efforts in raising the standards of urology to a high level which at that time was sadly needed. His son, Edward Keyes, who also received this medal, represented another era in the development of American urology. His was the period of progress in clinical urology which not alone broadened our field but established it as an independent clinical specialty. It was only last year that we lost him from our midst. We will never forget his genial personality, his keen wit and humor, his delightful as well as instructive discussions of medical problems, and his ever present spirit of progress.

We urologists can well be proud of the vast progress that has been made in our specialty during recent years. I well remember when I took over the field of urology at the Mayo Clinic forty-four years ago, I decided to visit Eastern medical centers in order to see what other urologists were doing. One urologist whom I visited advised me to choose some other specialty because, as he said, "Urology is now so well standardized." When one thinks of the many developments that have been made in our field since that time, one realizes the folly of believing that standardization in Urology ever has been attained or that it ever will be.

While the era of progress in clinical urology is not closed, nevertheless a new period is shaping in the future. It will probably be one based largely on research as carried on in physical, chemical and physiologic laboratories. It promises much for the future. In closing may I repeat a simile although often used, yet it seems to me, it expresses best the purpose of the Keyes medal. As I look upon the medal, it serves as a torch which will be carried on from one runner in the race of urologic progress to another. And when the next runner comes along, he will in turn extend it to younger men in endless vista of urologic progress.

Address prepared by Dr. Kretschmer and read by Dr. Charles C. Higgins.

CARCINOMA IN DIVERTICULUM OF FEMALE URETHRA

WM. NILES WISHARD, JR. AND MYRON H. NOURSE

From the Department of Genito-Urinary Surgery, Indiana University School of Medicine, Indianapolis, and Methodist Hospital, Indianapolis, Ind.

Diverticulum of the female urethra was not commonly referred to in the literature 15 and more years ago, but since then many reports on the subject have come into the record. Primary carcinoma of the female urethra, like that of the male, is an expanding topic, there being more reports of its instance in recent years than formerly. The appreciation of the possible existence of these lesions and the more prevalent use of the panendoscope doubtless explains their more frequent detection. We have not, however, been able to find in the literature a single instance of the simultaneous co-existence of a diverticulum of the female urethra and a primary carcinoma, nor of a carcinoma in a diverticulum (either sex). Doubtless this must have occurred, but we have been unable to find mention of it. It is not the purpose of this paper to give a comprehensive review either of female urethral diverticulum or carcinoma of the urethra, but to report a diverticular carcinoma.

Brack in his excellent recent article on carcinoma of the female urethra, makes no mention of co-existing diverticulum or carcinoma in diverticulum in any of the 338 cases of carcinoma reported to date. Counseller and Cook in separate reports of the 71 instances of diverticulum of the female urethra detected at the Mayo Clinic report no carcinoma, nor do Engel or Higgins in their separate and less recent articles dealing with the subject in patients at the Cleveland Clinic. Wharton, in a contemporary comprehensive report (1950) of the 30 cases of diverticulum of the female urethra at the Johns Hopkins Hospital between 1890 and 1949, gives an exhaustive study of female urethral diverticula, including many complications but makes no mention of carcinoma.

Although it is not the purpose of this report to deal with the subject in males, it is interesting to note that urethral diverticulum with carcinoma has likewise not been reported. Pate recently discussed urethral diverticula in paraplegics, and in his study reviewed the 197 recorded instances of diverticulum of the male urethra. No incidence of carcinoma was mentioned. Some time ago we had occasion to review the literature of primary carcinoma of the male urethra and found no instance of its existence in urethral diverticulum.

Wharton gives an excellent discussion of female urethral diverticula. He found that the size varied from 3 mm. to 8 cm. The wall of the diverticulum was thick if infected, as so many are. The surface membrane layer, if present, was of cuboidal or squamous epithelium. Two diverticula might be present in the same urethra. No co-existing vesical diverticula were found. All diverticula connect with the vaginal aspect of the urethra and may open into any part of the urethra and may have multiple orifices. Calculi, single or multiple, were present in 10 per cent. Spontaneous fistulas into the vagina were rare, though they have been reported following operation. Arthritis was relieved in 1 case by removal of a diverticulum from which gonococci were recovered.

Symptoms of bladder irritability and a palpable mass on the anterior vaginal wall are always present. Hematuria, retention and incontinence are rare though we have seen the former two in one and the latter in one case. Diverticula may be congenital or acquired and may therefore occur at any age.

Although carcinoma has not been reported in female urethral diverticulum, de la Peña in 1945 reported mucosal hyperkeratosis in a female urethral diverticulum, and Rebaudi, in 1937, reported a fibromatous polypus similarly located. To the already recorded complications and co-existing lesions, we wish to append a report of transitional cell carcinoma of a female urethral diverticulum.*

CASE REPORT

Mrs. S. B., a white housewife aged 39, was referred to our office by Dr. Harry Foreman November 16, 1949 because of almost total inability to urinate. She had had "bladder trouble" for years, and for the last 2 months severe burning, nocturia, frequency, difficulty in voiding, and a little bleeding. In 1947 examination elsewhere because of frequency, dysuria, nocturia, suprapubic pain, pyuria, and occasional hematuria revealed diffuse swelling below the urethra, compression of which expressed urine from an inflamed meatus. Cystitis was observed cystoscopically and "posterior urethritis with polyps" but no diverticular orifice was observed (though suspected). The patient herself had detected a mass between the urethra and vagina, and stated that it was painful and tender during intercourse. Several days before she was first examined by us she had aggravation of all her bladder symptoms, winding up on the morning we saw her with an almost complete retention. Past history and family history were otherwise irrelevant.

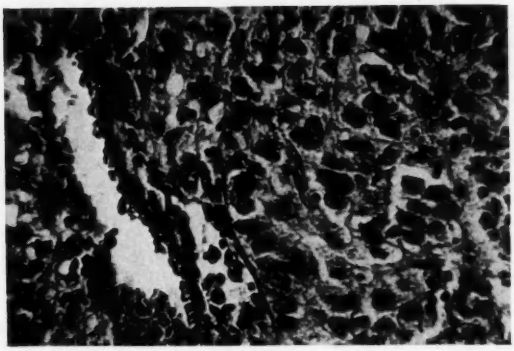
Abdominal examination was not remarkable save for suprapubic tenderness. No mass was present. Inspection of the introitus revealed a huge urethral meatus in the form of a vertical slit, somewhat edematous and a little cyanotic, behind which was a tender, diffuse mass bulging into the vagina. It was about 3 cm. in diameter, cystic in consistency, and occupied all the space from the meatus back to the base of the bladder. Urine dribbled out of the meatus, but pressure on the mass extruded viscid, blood tinged fluid, too thick for urine and not looking like pus. Her 12-ounce retention was relieved by catheterization, urinalysis being normal chemically, and microscopically showing many bacteria, pus and red blood cells. She was admitted on November 16 to the Methodist Hospital where further study revealed a blood pressure of 128/64, normal chest x-ray, negative Mazzini, 45 per cent phthalein (2 hours), urinalysis similar to the previous day, normal white blood count and red count of 2,860,000 with hemoglobin of 9 gm.

The next day cystoscopy revealed an elevated vesical orifice, normal bladder, normal original roentgenogram (save for gallstone) and pyelo-ureterograms. Segregated urines from each kidney were normal. Vaginal examination was the same as previously. Attention was given to sanguinous mucoid expressage from the meatus on urethral pressure. Panendoscopic examination of the urethra showed an aperture 5 mm. in diameter on the floor of the urethra to the left of

* Since this paper was prepared, a case has been reported by Hamilton and Leach (Arch. Path. **51**: 90, 1951) of an adenocarcinoma arising in a diverticulum of the female urethra.

the midline, a little closer to the vesical orifice than to the meatus. Mucoid tumor tissue was seen inside the sac. Loop biopsy was done without the use of any current. This showed a grade 1 transitional cell carcinoma. The patient was dismissed on November 18 to re-enter later for operation. No indwelling catheter had been used up to that time.

On November 21 she was re-admitted because of retention and severe hematuria. Two hundred and fifty cubic centimeters of clots were evacuated through the sheath of the electrotome and another biopsy done which showed a grade 3 transitional cell carcinoma. Thirty cubic centimeters of mucoid tumor tissue were extruded through the meatus by pressure on the vaginal side of the mass. The mass thus collapsed, but the vaginal integrity did not. An indwelling catheter



was inserted and no further bleeding ensued. Operative removal was elected, the diagnosis being carcinoma in a urethral diverticulum. The patient was warned that she might become incontinent.

On November 25, under spinal, pentothal, N_2O and O_2 the patient was placed in lithotomy position, vagina prepared, and further examination showed that the maximum bulge was apparent 1.5 cm. behind the meatus as a result of the collapse a few days before. Vaginal examination above the mass and bimanually was not remarkable. A linear incision about 4 cm. long was made over the bulging mass with division of the anterior vaginal wall. The diverticulum was dissected free from its surroundings and inadvertently opened on its vaginal aspect. Excision of the sac from the urethra left a considerable defect on the urethral floor very close to the bladder. This was closed with interrupted sutures in two layers. A 22F Foley catheter was anchored. Inspection of the specimen revealed it to be 3.7 by 2.8 by 0.8 cm. in size. The wall was not over 1.2 mm. thick. The lining epithelium was red in color, the rest of the sac being fibrous and smooth muscles fibres. There was low grade inflammatory infiltration, and in one area the stump of a previous neoplastic growth, section of which showed dark staining cells of large size penetrating into the muscular walls. No mucoid material was found in the sac after its removal as had been before. Final pathologic report of the removed sac by Dr. Horace Banks was "transitional cell carcinoma of urethral diverticulum (fig. 1)."

The patient had an uneventful afebrile convalescence. The catheter was removed on December 12, having been in 17 days. The patient had good control and was not incontinent. On December 16 vaginal examination revealed no further bulge. She was dismissed on December 17, twenty-two days after operation. Previously mentioned secondary anemia was corrected by transfusions though the hemoglobin was only 9.4 gm. at time of operation. Six months later it was 12 gm.

On January 3, 1950 the patient was seen at our office and a crypt found on the anterior vaginal wall at the site of operation too deep to be seen without a speculum. Urethroscopy on January 11 showed a urethrovaginal fistula just distal to the vesical orifice. No tumor was apparent. The urethral meatus remained very large, being a perpendicular slit 1 cm. long or more. Vaginal examination was normal (except for defect in floor of urethra) save for beginning stenosis of the vault which made the cervix hard to feel. The cervix and uterus were normal. Urinary control was excellent.

On February 28 the patient had a little stress incontinence, worse at night. On May 10 this had improved. The patient urinated without pain and in normal habit. There was no further bleeding. By this time the cervix could not be seen or felt, the upper vaginal vault apparently being closed.

On June 22 vaginal examination with a No. 28 panendoscope showed a small aperture not over size 5F, leading to the upper vault. Urethroscopy showed the urethro-vaginal fistula and nothing else.

On July 14, under pentothal, the vaginal adhesions were cut by Dr. J. K. Berman and the vagina opened. Granulation tissue was sectioned and showed no carcinoma. The cervix and uterus were normal. The vagina was dilated and packed with vaseline gauze which was removed a few days later. Urethroscopy was repeated with the same findings as previously.

On December 5 examination showed only the fistula. Urinalysis was normal. A little nocturnal stress incontinence remained.

SUMMARY

Diverticulum of the female urethra was recorded in volume 1 of the *Index Medicus* and thereafter but more frequently in recent years. Carcinoma of the female urethra now has been reported 338 times. No instance of carcinoma of a female (or male) urethral diverticulum has been found in the literature. A case of transitional cell carcinoma in a diverticulum of the female urethra is reported.

1711 N. Capitol Ave., Indianapolis 7, Ind.

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OBSERVATIONS ON HEMOLYSIS DURING TRANSURETHRAL RESECTION: THE EFFECTS OF UREA

C. D. CREEVY

From the Urological Division of the Department of Surgery, The Medical School, University of Minnesota, Minneapolis

The use of isotonic irrigating solutions has influenced the morbidity and mortality of transurethral resection of the prostate so favorably as to justify just one more report. Isotonic solutions are used for the following reasons.

Instant hemolysis accompanies the mixture of a small amount of blood with a large amount of water, and can be seen to occur during transurethral resection. The venous drainage of the prostate is very rich, as every retropubic prostatectomist knows. The largest veins are in and on the periphery of the prostate, and contain blood at very low pressure; they are necessarily cut at many points during an adequate resection.

That vesical contents enter the circulation during transurethral resection is proved by the following data:

1) Hemoglobinemia is common after transurethral resection with water. The free hemoglobin of the plasma postoperatively averaged fifteen times the preoperative level (Creevy). The postoperative level exceeded 51 mg. per cent in from 17 (Bunge and Barer) to 25 (Goodwin et al.) per cent. Hemoglobinemia does not occur when an isotonic irrigating fluid is used (Creevy, Nesbit, Goodwin et al., and others).

2) The blood sugar remains constant during transurethral resection with water, but rises to 2.4 times the preoperative level when four per cent glucose is used (Creevy). The rise in blood sugar is proportionate to the irrigating pressure (Jessop and Lane).

3) If the bladder is distended with neo-iopax for 5 minutes just after resection, then drained, and an x-ray film exposed 15 minutes later, a urogram will result if the renal function is adequate (Wear).

4) Bacteremia has been observed at the conclusion of transurethral resection in 60 per cent of 360 consecutive cases (Feeney and Creevy). Merritt found bacterial endocarditis 8 times in 7000 consecutive transurethral resections, and in 10 per cent of those with cardiac valvular disease who had prostatic resection.

The writer has been inclined to attribute the hemoglobinemia to blood hemolyzed in the bladder and driven into the circulation, because of the known tolerance of the normal dog and human to considerable quantities of intravenously injected distilled water (100 cc per kilo in the dog—Maluf). However, Credle, Warren, and Vest have measured the amount of free hemoglobin in the irrigating water used during resection, and have calculated that this could produce a maximum of 116 mg. per cent of free hemoglobin in the plasma. They have concluded that intravascular hemolysis must also be a factor in the hemoglobinemia.

The effects of hemoglobinemia are well known from intensive studies of the

"transfusion kidney." They include pigmented casts in the tubules and degenerative changes ranging from swelling and vacuolation to necrosis of the epithelium of the distal nephron (Lucké') or of the whole nephron (Bell). Identical changes occur after transurethral resection with water (Creevy, Goodwin et al., Credle et al., and others).

The mechanism which produces these changes is not clear. Baker and Dodds believe that the pigmented casts consist of acid hematin formed when the hemoglobin enters the acid urine of the tubules, which are thereby plugged. Since the experimental conditions on which these conclusions are based are highly artificial, and since the number of casts seen in many fatal human cases is too small to plug any considerable proportion of the nephrons, it seems more likely that the vascular spasm which signals the arrival of free hemoglobin in the kidney (Levy; Hesse and Filatov; Mason and Mann) damages the tubules by depriving them of oxygen (Maegraith, Havard, and Parsons). Anuria appears to result from complete reabsorption of the urine by the damaged tubular epithelium or by the interstitial tissue (Dunn, Gillespie, and Niven).

The symptoms of hemolytic reactions are well known; they include chills, cyanosis, and semistupor when severe. Anorexia, nausea, vomiting, oliguria or anuria, anemia and azotemia are common, and are followed by hemolytic jaundice and sometimes by hypertension. Pain in the chest and kidneys is concealed during transurethral resection by the anesthesia, and hemoglobinuria is hidden by the bleeding from the prostate.

The incidence of hemolytic reactions during transurethral resection with water is variable. The writer found postoperative azotemia in 13 of 106 consecutive cases, but only three were seen to be jaundiced and thus almost certainly hemolytic in origin. Goodwin et al. found 5 "lower nephron nephroses" in 69 cases. Two were fatal. This represents between 3 and 7 per cent of severe reactions. Many mild ones probably go unnoticed.

If hemolysis is so frequent, why is severe renal injury relatively rare? First, large veins near the capsule must be opened. Many resections are too conservative to do this. Second, levels of free hemoglobin high enough to injure the normal kidney are rare after transurethral resection. Flink found that a level of 3700 mg. per cent was necessary to damage the kidney of the normal dog seriously. Fairley and Bromfield observed levels of 3600 to 5100 mg. per cent in fatal blackwater fever. O'Shaughnessy et al. caused a 30 hour hemoglobinuria by injecting 50 gm. hemoglobin intravenously into a normal adult but observed no signs of renal injury. This probably represents a maximum level of 1400 mg. per cent, which would be very high for transurethral resection. The highest level observed by the writer was 900.

One must remember that the foregoing data refer to normal kidneys. Goodwin et al. have found that the injury to the dog's kidney by hemoglobinemia is intensified by senility and by hydronephrosis. Maluf has observed similar effects from surgical shock and from anemia. The prostatic patient rarely has entirely normal kidneys, such lesions as arterial and arteriolar sclerosis, hydronephrosis, pyelonephritis and even latent nephritis being quite common.

In addition, several factors associated with surgery may reduce the renal blood flow. Van Slyke et al. have seen cessation of the glomerular blood flow during surgical shock; Phillips et al. and Corcoran and Page have produced azotemia by bleeding dogs while maintaining blood pressure by administering fluids. Amorso has caused renal ischemia by distending repeatedly hollow viscera (uterus, bladder) in the experimental animal (Franklin). Sudden bacteremia may certainly cause renal vasospasm and injure the tubules directly as well.

Thus it is certainly a question of the free hemoglobin reaching, not a normal kidney, but one damaged by pre-existing disease and sensitized by acute impairment of its circulation and, at times, by sudden bacterial invasion. Extremely high levels of hemoglobin would appear to be unnecessary in such circumstances.

Since there is no dependable treatment for hemoglobinuric nephrosis, prevention is the obvious solution. That this may be achieved by the use of isotonic solutions of poor electrolytes has been proved by Creevy, by Nesbit, by Garske et al., by Goodwin et al., and by others. Four per cent glucose, 1.1 per cent glycine, and 3 per cent mannitol are equally effective.

Ebert has suggested the use of 1.8 and later of 0.9 per cent urea; alleging that its hemolytic properties, which are well known, are of no consequence. Credle, Warren, and Vest have seen severe hemolysis follow its use. We have used it ten times at the University Hospitals, but have desisted because there was demonstrable hemolysis (25 to 250 mg. per cent—average 65) in every instance and, because one patient died of a hemolytic reaction, the residents then balked. It is impossible, therefore, to accept Ebert's conclusions. Perhaps his resections are more conservative than ours?

Objections to and substitutes for isotonic solutions have been suggested. It has been alleged that hemolysis can be prevented by using a "low" irrigating pressure. Since the pressure in the pelvic veins is very low, a pressure lower than that would not clear away arterial bleeding: one could not see.

It has also been suggested that one should stop operating when water is seen to enter the cut veins. This is wholly impractical, since the event may be overlooked, and since the use of isotonic fluid obviates interrupting the operation.

It has also been said that the solutions coat the lenses and interfere with vision. This does not occur if the instruments are washed between operations.

Rolnick et al. have claimed that the isotonic solutions blur vision so much that operation is impractical. It is true that blood forms a transparent solution with water and a translucent one with isotonic agents, but one soon learns to compensate for this by holding the lens closer to the objective. Our residents do not appear to be handicapped while learning the operation with isotonic agents.

Periodically someone says that there must be "some other factor than hemolysis" concerned in these reactions. Burning by diathermy is mentioned, but the burn is too small to produce significant hemolysis, since the use of isotonic solutions prevents hemolysis despite the use of diathermy.

Most conclusive proof of the value of these solutions is to be found in the satisfying reduction of mortality which has accompanied their use. Two associates (E. A. Webb and B. A. Smith, Jr.) and I have performed transurethral resection

with isotonic irrigating fluid in 1273 consecutive patients between July 1946, and March 15, 1951. Nine deaths occurred in the hospital (0.7 per cent). The last 3 deaths occurred between 40 and 55 days after operation from coronary thrombosis. One was in the hospital continuously because of cardiac decompensation (C.D.C.); the other two had returned because of late postoperative bleeding and then succumbed (E.A.W. and B.A.S.).

During this same period the residents at the University Hospital have operated upon 744 patients with 16 deaths (2.2 per cent) while learning the operation. This makes a total of 2017 cases with 25 deaths or 1.23 per cent.

CONCLUSIONS

The use of isotonic irrigating fluid during transurethral prostatic resection has, by preventing hemolysis, yielded a striking reduction of mortality (0.7 per cent in 1273 consecutive cases by experienced resectionists).

The use of urea as an irrigating fluid appears to be dangerous because of its hemolytic properties.

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LEIOMYOSARCOMA OF THE KIDNEY

HERMAN L. KRETSCHMER*

From the Presbyterian Hospital of Chicago, Ill.

Leiomyosarcoma belongs to the group of very rare malignant kidney tumors. Because of its rare occurrence, it receives but scant attention in the average textbook. A careful review of the literature since 1929 reveals the reports only of 14 cases. Several hundred letters were sent to outstanding urologists. Replies were received from 50, none of whom had ever seen a patient with this condition.

Because of its rare occurrence, I wish to report the following case:

CASE REPORT

M. R., a white man aged 62 years, was admitted to the hospital on March 22, 1950. He was discharged April 5, 1950. An operation for a right inguinal hernia was performed several years ago. In 1946 he had a transurethral resection for benign prostatic obstruction from which he made an uneventful recovery. In December 1949, he experienced attacks of sharp intermittent pains in the right side of his abdomen. A diagnosis of duodenal ulcer was made and he was placed upon ulcer management with complete relief of pain. One week before admission to the hospital he had an attack of painless hematuria. The hematuria gradually diminished and the voided urine upon admission to the hospital was normal.

The physical examination was negative except for the presence of an enlarged mass in the right upper quadrant of the abdomen which was not tender and moved with respiration. The blood count and urinalysis were normal. The Kahn test was negative. The rectal examination was negative.

An excretory urogram showed that the left kidney was normal. The right kidney had a filling defect compatible with tumor.

Cystoscopic examination was negative. The urine from the right and left kidneys were free of pus, sterile upon culture, and negative on gram stains. The nonprotein nitrogen was 36 mg. per cent.

A right nephrectomy was done March 24, 1950 under pentothal sodium, nitrous oxide anesthesia. Delivery of the kidney was difficult because of adhesions. The twelfth rib was resected.

Microscopic diagnosis by Dr. George M. Hass: Leiomyosarcoma of the kidney with compression atrophy (fig. 1).

The patient made an uneventful convalescence. Recent examination on January 10, 1951 was negative.

DISCUSSION

A careful perusal of the literature since 1929 revealed the following reports of leiomyosarcoma of the kidney. Unfortunately many of the cases were reported in a very brief manner, as simple case reports, often lacking important details and but few carry any discussion of the subject.

* Deceased

Berry (1929). Female, 26. She first noticed pain in the right loin, and frequency of urination 14 months previously during the seventh month of her first pregnancy. After the child was born, symptoms continued. Exploratory operation revealed a leiomyosarcoma of the kidney involving the lower pole of the right kidney. Nephrectomy eight months later. Patient was still well two and one-half years later with no evidence of metastases.

Crosbie and Pinkerton (1932). Female, 35. She had moderate pain in the lumbar region with frequency of urination. Operation revealed a malignant leiomyoma of the kidney.

Swan (1933). Male, 71. Leiomyosarcoma of left kidney. Patient was still well 12 months after nephrectomy.

Cooke (1933). Female, 60. During exploratory operation patient died. The autopsy showed a malignant leiomyoma of the kidney, with metastases to omentum, peritoneum, and liver.

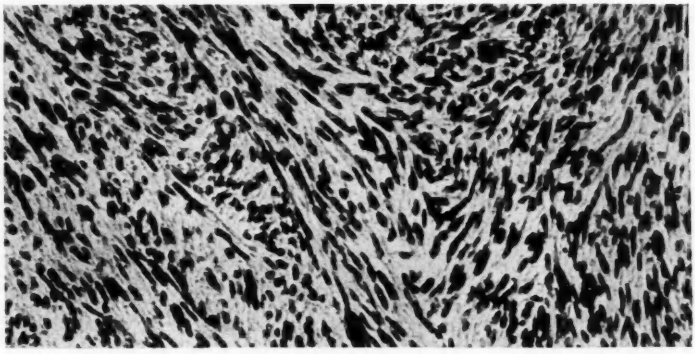

FIG. 1

Smith, G. G. (1935). In his series of 40 cases of tumor of the upper urinary tract which came to him for operation, there was one leiomyosarcoma of the kidney. The patient was alive and well 18 months after operation.

Patch (1937). Male, 55. He had pain in the right loin; passage of blood clots. Nephrectomy for malignant leiomyoma of the kidney with extension into the renal vein.

Mintz (1937). The records of the Massachusetts General Hospital revealed the following 4 cases of leiomyosarcoma of the kidney:

Female, 46. Pain and vomiting 3 weeks; palpable mass in right side. Operation. Lipoleiomyosarcoma of the kidney. Recovery.

Male, 37. Vomiting; urine red; abdominal mass. Exploratory operation at which diagnosis of polycystic disease was made. Death 5 days later. Author showed *bilateral* lipoleiomyosarcoma of the kidneys.

Female, 45. Pain in left back and lower left abdomen; frequency of urination; palpable mass in left kidney region. Nephrectomy for leiomyosarcoma of left kidney. Patient died.

Female, 41. Pain in right groin and flank; movable mass in right upper quadrant. Right nephrectomy. Leiomyosarcoma. Patient recovered.

Tetelman and Lisa (1945). Autopsy findings in patients, aged 86 and 74. Leiomyosarcoma of the kidney.

Shaheen, Cassano and Lisa (1944). In 1923 cases of primary tumors of the kidney among 5,100 necropsies, there was only one case of a leiomyosarcoma. This tumor did not produce symptoms.

da Silva Horta and Madureira (1946). Male, 64. Grawitz tumor of the kidney with sarcomatous, leiomyomatous and chondromatous structure.

A review of the cases showed that the youngest patient was 26 years of age, and the oldest 86 years of age. Three cases occurred in the decade from 40 to 50 and three, including my case, occurred in the decade from 60 to 70. In one case reported by Mintz, the lesion was bilateral.

122 S. Michigan Ave., Chicago 3, Ill.

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CONSERVATIVE AMPUTATION OF THE PENIS FOR CARCINOMA

ARCHIE L. DEAN

From the Department of Urology, Memorial Hospital, New York, N. Y.

The purpose of this paper is to describe a simple but adequate procedure for conservative amputation of the penis which the writer has employed with few modifications in about 150 cases. The operation is based on the fact that penile carcinomas, like other epidermoid cancers, metastasize by embolism and, therefore, all of the primary growth can be removed when amputation is performed 1.0 to 1.5 cm. proximal to any visible or palpable evidence of disease. Enough of the penis thus is conserved to direct the urinary stream and occasionally to perform coitus.

Since the operation is performed quickly without shock, no special general preparation of the patient is required. Cleansing the growth with soaks in warm medicated solutions, formerly the principal preoperative measure, is now but a supplement to use of chemotherapy and antibiotics. The amputation can, therefore, be done soon after the diagnosis has been established by microscopic examination. When the biopsy is performed, one should take the opportunity of demonstrating that the penis is involved with tumor because occasionally only the prepuce is affected and no more than a circumcision may be needed.

A low spinal anesthesia is used. After the usual skin preparation, a tourniquet is placed about the base of the penis. A hand towel is then folded over the infected ulcerated tumor. The edge of this towel may be carefully fixed with clips about 1.5 cm. proximal to the growth to indicate the line of incision (fig. 1, *A*). With a large scalpel, a guillotine amputation is quickly performed and the foul growth, still securely enclosed in the sterile towel, is carried from the operating room. The subcutaneous dorsal vessels now should be ligated with a suture ligature but usually no other vessels need attention at this time.

With the penis clearly exposed in cross section (fig. 1, *B*) one should search for residual tumor. If present, it is pearly gray or pale yellow in color and is most likely to be in lymphatics accompanying the larger veins. I have never made such a discovery and it must be rare because local recurrences are so uncommon. It would, however, call for amputation at a higher level.

The corpus cavernosum urethra is now dissected from the corpora cavernosa penis for a distance of 1.0 cm. (fig. 1, *B*). At the proximal end of this separation, a double ligature of No. 1 chromic catgut on a straight needle is passed through the septum between the corpora cavernosa penis. When the needle has been cut from this doubled suture, a single suture can be tied around each corpus cavernosum (fig. 1, *C* and 2, *A*). The tourniquet is now removed. A few insignificant vessels may require clamping and ligating but the two urethral arteries which may spurt from their positions at 3 and 9 o'clock respectively in the wall of the corpus cavernosum urethra are temporarily ignored.

A slit nearly 1 cm. long is now made in the dorsal aspect of the corpus cavernosum urethra (fig. 2, *A*) and the entire cut edge of this structure is joined to the

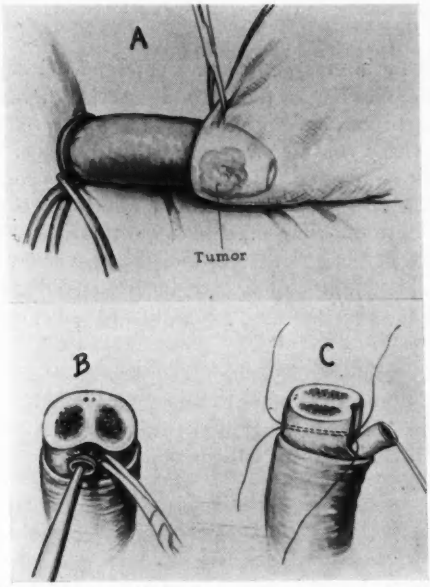

FIG. 1. *A*, with a tourniquet applied to base of penis, a towel is folded over growth and is fastened so that its edge indicates the line of amputation. *B*, penis is seen in cross section after amputation of tumor bearing portion. Dissection of corpus cavernosum urethra is about one-half completed. Urethral arteries are located in this structure at 3 and 9 o'clock respectively. *C*, corpus cavernosum urethra has been freed sufficiently and a doubled ligature has been passed through the septum between the corpora cavernosa penis.

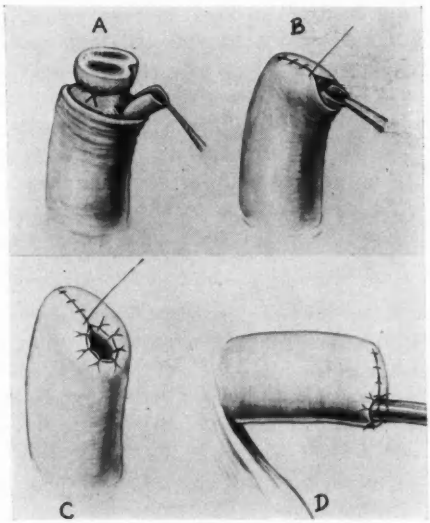

FIG. 2. *A*, corpora cavernosa penis have been ligated and the corpus cavernosum urethra has been slit dorsally to provide an adequate urethral meatus and to avoid urethral arteries. *B*, skin edges have been approximated over stump of corpora cavernosa penis and sufficient has been left for attachment to entire cut edge of corpus cavernosum urethra. *C*, stump has been covered and urethra fixed to skin. *D*, indwelling catheter is used for about 4 days to keep wound dressing dry.

cut edge of the skin by interrupted sutures of No. 4 chromic catgut. Some of these sutures stop the bleeding of the urethral arteries (fig. 2, *B* and *C*).

The stump of the corpora cavernosa penis is now covered by joining the remaining skin edges with a continuous suture of plain catgut. As shown in figure 2, *B*, the stump may be covered before the urethra has been sewn to the skin. This does not alter the operation but it is more difficult to first cover the stump and leave just the length of skin needed for apposition to the urethra than it is to first join the edges of these structures and then cover the penis stump with the skin which remains. An indwelling catheter is inserted and is used for about 4 days or until there is no further need for a dressing which might interfere with urination.

These patients are confined to bed only until they recover from the anesthetic. They have little discomfort and there has been no mortality. In but one instance was there a recurrence of tumor in the operative site. A second conservative amputation was performed and this patient now has been free from all evidence of disease for 8 years.

RENAL HAMARTOMA (ANGIOMYOLIPOMA): REPORT OF THREE CASES

CARL RUSCHE

Hamartomas have been reported in most organs of the body, perhaps the most common site being the lung with renal involvement of infrequent occurrence. The earliest recognition of this tumor is credited to Chiari (1883) who termed it lipo-chondro-adenoma. Albrecht (1904) called this complex structure hamartoma, or "error tumor," and described it as a lesion formed by normal tissue elements which are abnormal only in their quantitative value. The deduction to be drawn from histological examination of these formations is that they have originated in an abnormal mixing of the tissue elements; or from disturbance in their development.

From the available data, scientific textbooks and a review of the world literature, renal hamartomas have been considered a comparatively rare lesion, although the actual index of incidence is believed to be much higher because many of the lesions are never diagnosed. Ordinarily, they are incidental findings at postmortem. Friedman is of the opinion that many of these tumors, which generally are only a few millimeters in diameter, go unnoticed in histopathologic examinations of renal specimens removed surgically and at autopsy. Thorough investigation of minute filling defects revealed in pyelograms might disclose the presence of these neoplasms in some instances.

Von Litchenberg, Voelcker and Wildbolz (1926–1929) reviewing the world literature, recorded no instance of renal hamartoma. The few cases of recent date which have been reported may be of noteworthy significance. Moolten (1942) reported an occurrence in a 15 year-old girl; Mallory (1949) observed one in a woman 39 years of age; both cases were diagnosed as a result of renal symptoms. One of the cases which Inglis (1950) reported in a 56 year-old woman manifested clinical symptoms; the other case, a 41 year-old woman, was an incidental postmortem finding. In the Registry of the Armed Forces Institute of Pathology there are 52 cases of renal hamartoma, all occurring in males, 44 were found at autopsy; and 8 manifested clinical symptoms.

ETIOLOGY

From the varied histologic formations, the presence of abnormal and normal tissue, it is impossible to determine whether hamartomas should be classified as an anomaly of development, or a true neoplasm. Although these lesions are composed of mixed elements they are not true teratomas, which contain other elements such as hair, squamous epithelium, and nerve cells; none of which are present in hamartomas. The lack of mitotic figures, the noninvasiveness and nondifferentiation, and the apparent absence of metastases in the cases which have been studied, are characteristic of a benign tumor.

Inglis has suggested tissue predisposition from germinal transmission as a causative factor. It is assumed that these tumors have their origin in aberrant

anlagen and arise from fetal nests of cloacal tissue. The cloaca of fetal life eventually separates and differentiates into the urinary passage anteriorly and the bowel posteriorly two ways, into intestinal epithelium, or into transitional epithelium. Friedman and Ash concluded: "The patches of intestinal epithelium which are not infrequently encountered in the bladder may be derivatives of embryonic cloacal rests. Similarily, the presence of intestinal mucosa and well developed Brunner's glands in the renal pelvis can only be explained by assuming that a rest of tissue with the capacity to form enteric structures was displaced from the cloaca to the ureteral bud."

CLINICAL FINDINGS

Comparatively little is known of the clinical course of these lesions, which are characterized by their asymptomatic behavior. When symptoms occur, there are no recognizable manifestations which differentiate them from other renal tumors. Urinary symptoms are not a constant factor. A large renal mass due to a retroperitoneal hematoma or hematuria may be the only symptom. Surgical exploration, subsequent to urologic studies, is the recommended procedure.

Bell (1946) states that in one-half of the cases of tuberous sclerosis multiple benign tumors are present in the kidney. The co-existence of the tuberous sclerosis complex was present in the case reported by Moolten; one of the cases presented by Inglis; and occurred in 50 per cent of the cases registered with the Armed Forces Institute of Pathology. However, these tumors may be associated with or occur independently of tuberous sclerosis.

Tuberous sclerosis was described by Bourneville and Brissaud (1880) in feebleminded children with epilepsy and progressive mental deterioration. Since the term tuberous sclerosis refers primarily to the changes in the brain, the broader term tuberous sclerosis complex is therefore employed to denote the co-existence of homologous changes in other organs, notably the heart, kidneys, retina, and skin.

Moolten states: "The clinical diagnosis is possible if two or more of the following features can be demonstrated: mental retardation, epilepsy, adenoma sebaceum, phacoma of the retina, multiple mixed tumors (hamartomas) of the kidney, and a familial history of the disease." A very excellent survey of the subject tuberous sclerosis may be found in the paper by Critchley and Earl (1932).

I wish to report a case of suspected right renal apoplexy which on exploration proved to be a renal hamartoma. Two of my colleagues, Fuller and Preuss, have accorded me the privilege of including two of their unpublished cases diagnosed at postmortem.

CASE REPORTS

Case 1. M. W., a white woman 23 years of age, who had enjoyed excellent health prior to and during her first pregnancy, was delivered of a normal 9-pound baby, December 20, 1949. It was a rapid delivery, requiring no unusual manipulation other than low forceps.

Approximately 12 hours postpartum, the patient was awakened by a dull pain in her right side. She complained of shortness of breath, palpation, pallor and sweating. The symptoms were in keeping with internal hemorrhage. The physical examination demonstrated a large mass in the upper right quadrant of the abdomen, which did not fluctuate, was moderately firm in consistency, and only slightly tender.

The prothrombin time was 56 per cent of normal; hematocrit test was 22; and clot retraction was normal. The urine was grossly clear but loaded with red blood cells. The white cell count was 15,800; erythrocytes 2,800,000; and the hemoglobin was 9 gm.

Cystoscopic examination the following day revealed a normal bladder. Ureteral catheters were readily passed to each renal pelvis. Indigo carmine injected intravenously appeared in four minutes from each kidney, with marked reduction in dye concentration from the right. Roentgenograms disclosed a soft mass in the right renal area. The right pyelogram showed displacement toward the right upper quadrant of the abdomen with distortion of the lower calyx. Only the upper and middle calyces were visualized. There was medial displacement of ureter and obliteration of psoas shadow (fig. 1). The left kidney and ureter showed no departure from normal.

The blood studies showed no improvement following two blood transfusions and a course of vitamin K therapy. Clinically, the mass in the right renal area had undergone no change in two weeks. The patient continued to complain of slight abdominal discomfort, and microscopic hematuria.

Retrograde pyelograms made on the fifteenth day postpartum showed the same changes demonstrated 2 weeks previously (fig. 2). The preoperative diagnosis was renal apoplexy probably associated with renal neoplasm. The possibility of tumor was seriously considered.

On the seventeenth day postpartum, a surgical exploration was carried out. Upon exposure of the kidney, a large, reddish mass, apparently a large hematoma, was encountered. Following the removal of the organized blood clot, the kidney was readily palpated, the lower pole was irregular, firm, and enlarged consistent with neoplasm. Nephrectomy was performed. The gross specimen consisted of the right kidney measuring 17 by 15 by 16 cm. with 13 cm. of the ureter attached. The lower one-half of the kidney surface was irregular, rough, and presenting numerous large cavities filled with hemorrhagic material (fig. 3). On section, a discrete nonencapsulated yellowish tumor mass with marked necrosis and hemorrhage occupied the lower half of the kidney. The kidney pelvis was not involved by the tumor mass. The upper pole of the kidney appeared normal (fig. 4). The histopathologic diagnosis was renal hamartoma. Microscopic sections were submitted to Friedman, formerly with the Army Institute of Pathology, for confirmation of diagnosis.

Pathological report (Friedman): "The tumor consists of three intermingled components; fat, blood vessels and bundles of smooth muscle. Much of the fat is adult adipose tissue but there are many clusters of embryonal fat cells particularly about the vessels. The vessels are predominantly thick-walled, small arteries

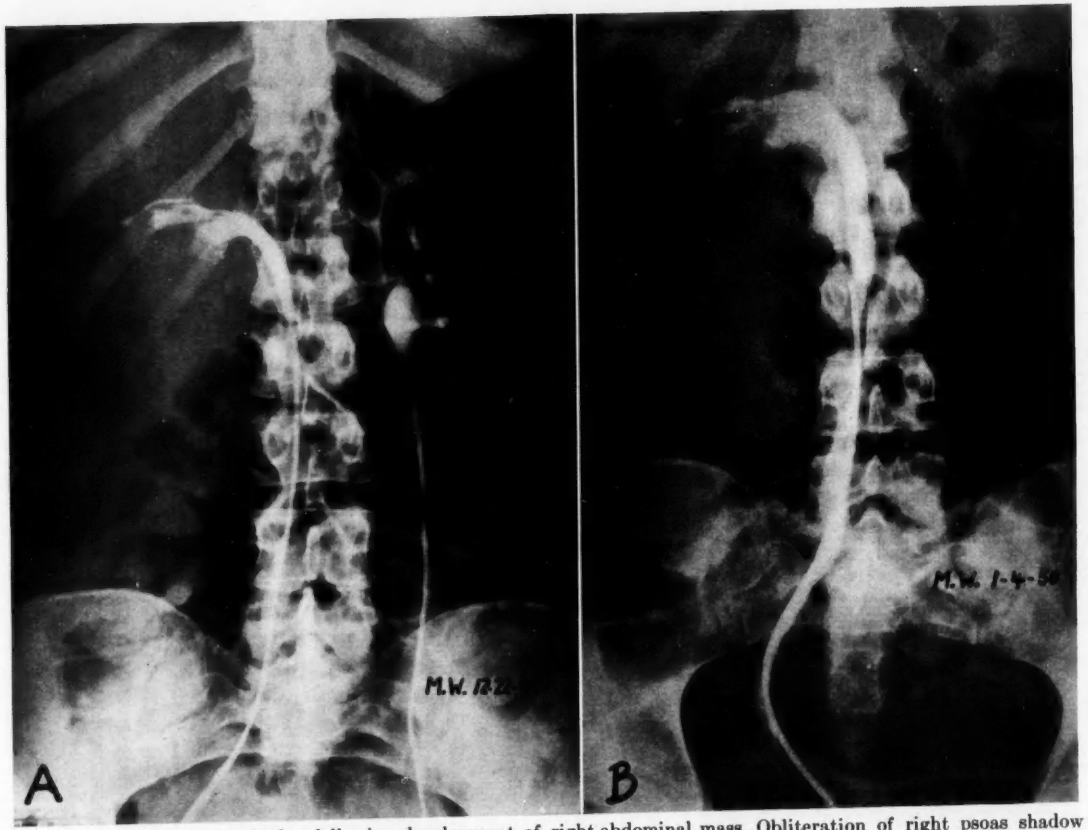

FIG. 1. *A*, pyelogram made day following development of right abdominal mass. Obliteration of right psoas shadow Distortion of middle and lower calyces, and medial displacement of right ureter. *B*, right pyelogram 15 days later. showing same filling defect.

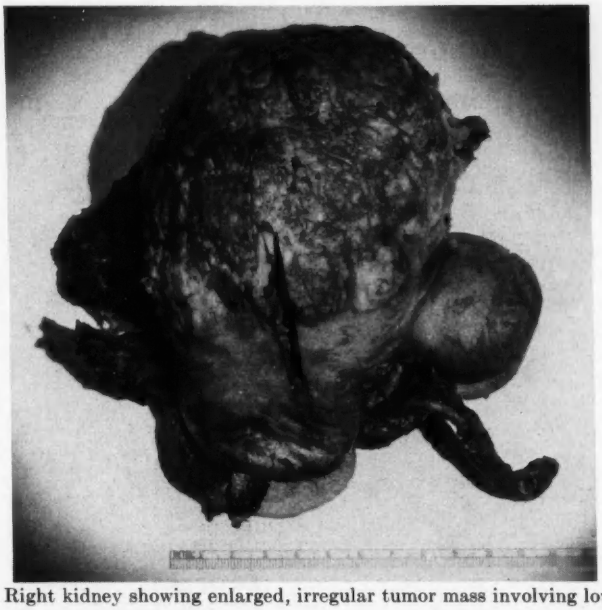

FIG. 2. Right kidney showing enlarged, irregular tumor mass involving lower pole.

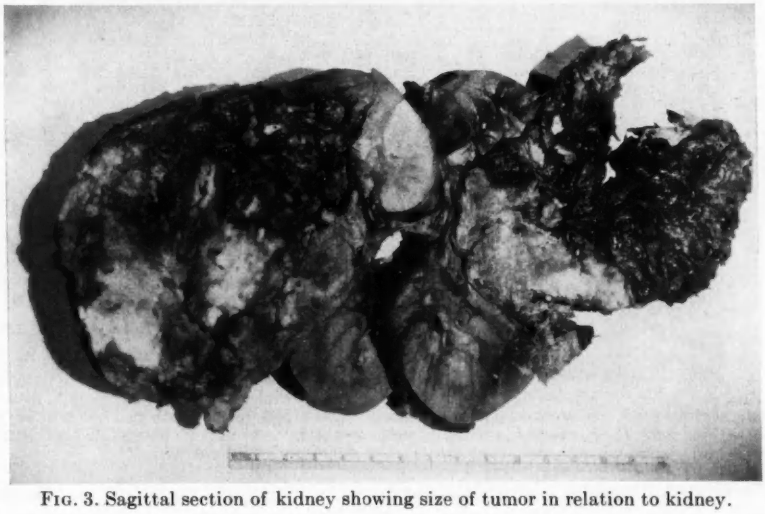

FIG. 3. Sagittal section of kidney showing size of tumor in relation to kidney.

and arterioles. There is intimal sclerosis and the muscular layer is especially well-developed. In many places the vessels lie in the fat where they are surrounded by collars of immature muscle which streams out into the surrounding tissue. There are areas of necrosis and inflammation. The border between the tumor and

FIG. 1. *A*, pyelogram made day following development of right abdominal mass. Obliteration of right psoas shadow. Distortion of middle and lower calyces, and medial displacement of right ureter. *B*, right pyelogram 15 days later, showing same filling defect.

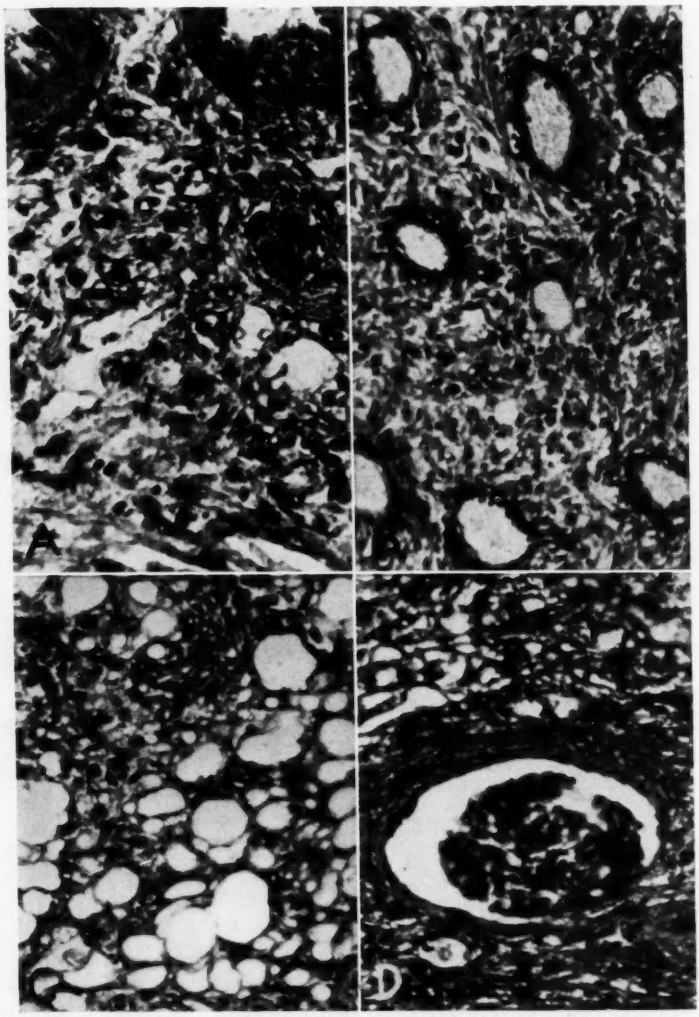

FIG. 4. Case 1. *A*, shows marked proliferation and thickening of blood vessels, muscle fibers, and fat cells. ×150. *B*, compressed tubules and blood vessels with marked leukocytic infiltration. ×72. *C*, number of mature fat cells and strands of muscle fibers. ×72. *D*, tumor has compressed renal parenchyma. Infiltration surrounding glomeruli. ×150.

the kidney parenchyma is well demarcated but there is no capsule. A few glomeruli and tubules are incorporated within the edge of the neoplastic tissue although this could not be interpreted as frank infiltration.

"The growth obviously falls into the category of the angiomyolipomas and sarcomas which are rare but characteristic *hamartial tumors of the kidney*". (figure 5—A, B, C, D).

An uneventful postoperative course ensued, and the patient was discharged on the twelfth day subsequent to the nephrectomy. Repeated examinations during the past 30 months have disclosed no evidence of the tuberous sclerosis complex. To date her second pregnancy of five months gestation has been uneventful.

Case 2. P. H., a white man, 50 years of age, was admitted to the hospital January 19, 1949, in a semicomatose state. Five days prior to admission the patient had a temperature of 103F, and complained of severe pain in abdomen following the taking of fluids.

The physical examination revealed a very dehydrated, apprehensive, and mentally confused patient. The temperature was 102.4F. The palate was covered by a dried, brittle substance. The heart sounds were loud and rapid, and there

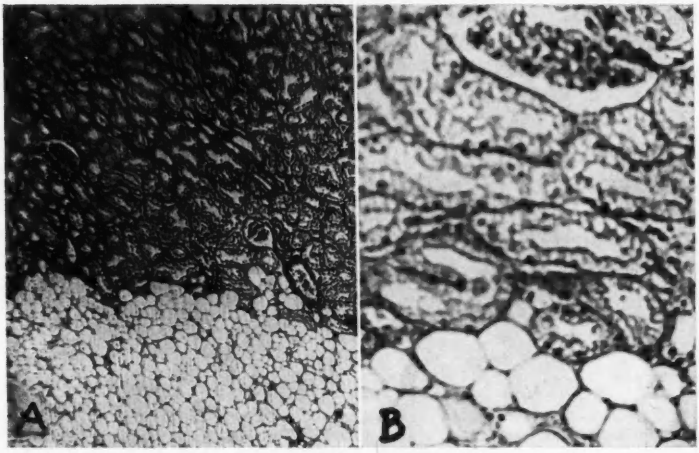

FIG. 5. *A*, hamartoma showing discrete tumor edge with apparent renal compression. Fat cells and renal tubules. ×300. *B*, same area with compression of tubules. ×150.

was a palpable thrill. Urinalysis showed specific gravity 1028, albumin 2 plus, occasional pus cells, a few red blood cells and rare hyaline cast. The clinical findings otherwise were within normal limits. Penicillin and streptomycin were administered for the rapidly progressive oral infection, which was believed to be a gangrenous stomatitis. The mental condition of the patient was considered to be a toxic psychosis. There were no symptoms, either in the present or past history referrable to the genito-urinary tract. Death occurred on the seventh hospital day.

Postmortem diagnoses: acute, nonspecific, membranous stomatitis, etiology undetermined; terminal acute bronchitis; lobular pneumonia; generalized atherosclerosis; moderate cerebral cortical atrophy; considerable leptomeningeal fibrosis; adhesive pleural fibrosis; atrophy of left testis; atrophy of right kidney; and *hamartoma of left kidney.*

The right kidney was found to be atrophied and its entire lower half was covered by a fatty substance suggesting a nonfunctioning organ. The left kidney

revealed the presence of multiple, sharply circumscribed and somewhat globular, soft, friable, opaque, yellow-brown tinted nodules which varied from 0.7 cm. to 1.5 cm. in diameter. These nodules, although sharply circumscribed, were not encapsulated. Approximately one dozen of these peculiar nodules were haphazardly distributed in the substance of the kidney. There was no deformity of the renal pelvis.

Microsections of the nodules disclosed nonnative tissue resembling adipose tissue of the adult type. The nuclei were abnormally conspicuous and hyperchromatic and showed more than normal variation in size and shape. The cytoplasm of these cells was occasionally not completely washed away, and certain cells were quite distinctly spindle-shaped and were arranged parallel with a vague tendency towards bundling. The vessels are thick-walled. In many places the vessels lie in the fat where they are surrounded by collars of immature muscle fibers (fig. 6—A, B).

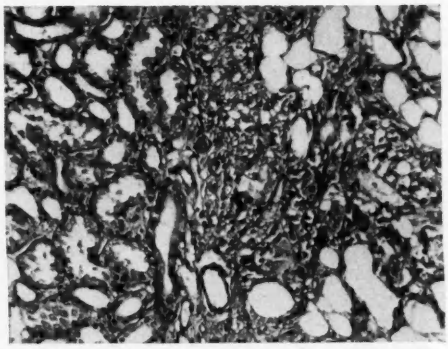

FIG. 6. Case 3. Hamartoma with compression of parenchyma. Sho wing fat cells, muscl fibers, and compressed glomeruli. ×72.

Case 3.—L. B., a woman 76 years of age, was admitted to the hospital March 13, 1949, and died 3 days later. Eight hours prior to admission she developed severe abdominal pain, associated with nausea and vomiting. As in the preceding case there were no genito-urinary symptoms. Physical examination revealed an acutely ill woman, in myocardial failure with generalized edema and ascites.

The postmortem diagnoses: acute bronchitis; lobular pneumonia; intestinal obstruction; atherosclerosis; cholecystolithiasis; *large (angiomyolipoma) hamartoma of the left kidney.*

Embedded in the substance of the lower pole of the left kidney was a sharply circumscribed but nonencapsulated globular tumor mass which measured slightly less than 4 cm. in greatest diameter. The opaque, yellow-gray tinted substance of this tumor is extremely friable. The microscopic sections showed a *renal hamartoma*, and the diagnosis was confirmed by the Tumor Registry of the California Society of Pathologists, and California Cancer Commission. The tumor revealed a mixture of several kinds of unripe tissue of mesenchymal origin. There

was present smooth muscle, numerous small and large thick-walled blood channels and fat cells of the adult type (figure 7).

COMMENT

Three cases of renal hamartoma were reviewed, one surgically diagnosed and the other two were incidental postmortem findings. The tuberous sclerosis complex was not associated with these 3 cases. However, isolated hamartomas of the kidney occur independently of tuberous sclerosis complex. The medullary "fibroma" is well-known. In addition, solitary lesions of the cortex have been reported under the name benign mixed tumor. They are generally small and are classified by whatever component is predominant, as hemangioma, lipoma, myoma, fibroma, etc. They are found mostly in adults, and except for infrequent hematuria they are symptomless.

As some patients have been known to develop clinical symptoms of tuberous sclerosis some years after the diagnosis of renal hamartoma, a detailed examination of the patient treated surgically was recently carried out. Thirty months following the diagnosis there is no evidence of the disease.

The lesion must be kept in mind in the differential diagnosis of renal neoplasms. Renal hamartoma is an interesting and rare tumor. Unless the lesion is large with associated spontaneous hemorrhage, it is unaccompanied by symptoms and consequently without clinical significance. The diagnosis may seem to be only of academic interest; nevertheless, the benign nature of the growth emphasizes its importance of prognosis.

1680 N. Vine St., Hollywood 28, Calif.

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DISCUSSION

Dr. William J. Baker (Chicago, Ill.): It is noteworthy that after 29 years in a large charity hospital and 25 years in a large private hospital, only one instance of sarcoma of the kidney in an adult has been seen. Dr. Kretschmer has reported an instance of renal leiomyosarcoma in an adult. I wish to report an instance of reticulum cell sarcoma of the kidney in an adult who was seen during the past year. A 65-year-old white woman was healthy until 1 month before her hospital admission. Her first complaint was flatulence and change of bowel habits. A complete physical survey at that time disclosed amoebiasis. Therapy was instituted. She lost 20 pounds of weight during the next four weeks. She had a daily low-grade fever. She became very tired and weak and she disliked food.

On admission the only findings were secondary anemia, daily low-grade fever and tenderness in the region of the left kidney. The bone marrow study was normal. Her sedimentation rate was 124 mm. after 1 hour. Ureteropyelograms showed an abnormal form of the collecting system of a large left kidney, which was then palpable. No evidence of metastases could be found. The urine contained no pathological elements. Without preoperative roentgen therapy, a large, fairly mobile left kidney and 9 inches of the ureter were removed. The left suprarenal gland seemed normal and it was left in place. No palpable lymph nodes were present.

Examination of the renal mass disclosed just a rim of compressed kidney and a large light gray tumor. Microscopic study showed this tumor to be a reticulum cell sarcoma whose cells had invaded the remaining renal tissue.

The postoperative course was uneventful. She received 32 deep roentgen therapy treatments and went home. After 8 weeks she became apathetic. She ran a low-grade daily fever and would not eat. She was again admitted to the hospital and she died after 4 days.

A complete autopsy by Dr. Edwin F. Hirsch of St. Luke's Hospital, Chicago showed a small metastatic tumor nodule in the right ovary and a larger one in the right adrenal gland. There were no other metastases. The bed from which the anaplastic kidney had been removed contained no cancer cells, and there were no metastatic regional lymph nodes. Low-grade fever and weakness were the presenting and final symptoms of this entity.

One could believe that this tumor was related to the group of cancer-like blood dyscrasias which produce fatal generalized systemic pictures.

Dr. David M. Davis (Philadelphia, Pa.): I should like to discuss Dr. Creevy's paper. I confess, as time goes on, I am more and more puzzled by the contributions in regard to prostatic surgery. I think this discussion should be continued until some kind of a conclusion can be reached, and it should be continued in an atmosphere of complete objectivity, without any emotional content whatever.

In a situation where all cases of a disease are treated by the same surgical method and where, particularly in regard to prostatic surgery, we have had a

number of articles from different sources suggesting that prostatic operations may be carried out without much regard to the state of the kidneys, allowing the kidneys, if they will, to recover their integrity after the operation instead of before; one wonders if the old criteria reached with such pain and travail years ago for kidney integrity before operation are being ignored too much at present.

Certainly, they are not being ignored by some operators. Dr. Shivers, of Atlantic City, is one who has advocated on many occasions that careful attention be given to kidney integrity before operation. He advocates for this purpose intravenous urography. Certainly, we have found this to be of great value in many instances. We have not hesitated to perform suprapubic cystostomy and wait as much as six to twelve months for kidney integrity to be restored before operating upon the prostate.

That being the case, one wonders if, perhaps, in their enthusiasm for certain procedures, some have gotten a little away from close attention to the old principle of "non nocere," in other words, to consider only and all the time, the welfare of the patient and to do nothing which may harm him. In that respect I must throw modesty aside for a moment and refer to a compilation of my own personal cases of prostatic surgery. The report is nearly finished. Up until the present time they include, plus or minus a few, 100 conservative perineal prostatectomies, 14 radical prostatectomies for early carcinoma, a few suprapubics, perhaps half a dozen, one retropubic, and 300 transurethral resections, all consecutive, without a death and without any serious or alarming illness. This was accomplished only by the most meticulous attention to every possible detail.

When the permissible mortality is as low as it is in prostatic surgery, nothing can be neglected; nothing can be left to chance. Of course, chance might very easily have carried off one or more of these patients, but the above figures show what actually happened. I maintain that even with good luck it would not be possible to set such a good record unless one did pay attention to every possible source of trouble.

The 300 transurethral resections were done with water as the medium. We found an extremely slight degree of hemolysis in certain cases where, for one reason or another, we took specimens of blood afterwards. Generally speaking, none was seriously ill, and none had what we could call lower nephron nephrosis. They all survived and left the hospital in good condition.

We, of course, did not operate in that manner on the very large prostates. They were done by prostatectomy. Perhaps it might be claimed that we did not do radical transurethrals, but we did apply the most meticulous criteria for success that we knew about; namely, before we got through with them, they had to be able to void their urine at a rate of 20 cc per second or better, they had to empty their bladders, the bladder capacity had to be normal, and the urine had to be sterile. I do not see how you can go much further than that.

In order to maintain this record, we had to do repeat resections on 10 per cent of the cases. That is about the same experience which everyone else has had.

People who have had prostatectomies are in the hospital little more than two weeks and often a good deal less than that. By performing such an operation it

is possible to avoid all danger of hemolysis or of overloading of the vascular system with fluid, so why not do it?

DR. FLETCHER COLBY (Boston, Mass.): My discussion is in connection with Dr. Rusche's paper. We have had only one instance of hamartoma of the kidney which has been reported. I thought you might be interested in seeing the slide which I have with me. This was a 39-year-old woman who had, as her first symptom, profuse bleeding from her right kidney. The right kidney was exposed through a thoraco-abdominal incision. A mass was felt in the pelvis of the kidney and since a primary tumor of the renal pelvis was suspected, a nephro-uretectomy was performed. Within the renal pelvis was a large, soft mass which rose from a slender pedicle. Histological examination reported the presence of glands similar to those of the intestinal tract. The diagnosis was hamartoma of the kidney.

DR. GEORGE LIVERMORE (Memphis, Tenn.): Certainly we become befuddled when we hear that one man uses distilled water without deleterious effect while another has so many reactions he uses glycine. Dr. Cook at Mayo Clinic uses distilled water and gives no preoperative medication, yet we know his mortality is less than 1 per cent.

I have had less reactions and less mortality since giving penicillin or streptomycin with gantrisin before and after operation, using glycine as the irrigating fluid during the resection.

I should like to refer to Dr. Dean's paper. A few years ago someone in this Association suggested turning back a cuff of the mucosa of the urethra. This seemed to prevent contraction of the meatus which so often occurs following this operation.

DR. MONTAGUE BOYD (Atlanta, Ga.): Dr. Dean has brought up a very interesting subject, but his views seem to be at variance with mine and I thought I knew something about carcinoma of the penis.

My experience has been that the laboratory has reported involvement of lymphatic glands, in carcinoma of the penis, where gland dissections have been done. Some years ago, I went through the literature extensively, and the conclusion in the literature, as far as I can recollect, is that the lymphatic glands were frequently involved in carcinoma of the penis and that was the reason for radical resection of the lymphatic glands.

I do not know if Dr. Dean was talking about some specific type of carcinoma of the penis or not, but there is no question in my mind about this: That resection of the glands of the groin has resulted in a better mortality rate in treating carcinoma of the penis. My experience indicates that clearly.

I have been told that in New York there has been a tendency toward conservatism in resection of carcinoma of the penis. I have wondered why that was. The tendency, I understood, was to treat the glands of the groin with radium after the glands seemed large enough to suggest involvement. That does not seem to me to be an adequate answer when you are dealing with a carcinoma which may be cured by radical measures.

There is always this swing from radicalism to conservatism. We went through

that with prostatic resections. When transurethral resections came out, we started to swing back toward conservatism, and now we are going again into more radical operations such as retropubic prostatectomy.

Unless there is some good evidence presented to prevent us from doing resections of the glands of the groin in the more extensive cases, I think that it ought to be continued whenever indicated.

With reference to the handling of the urethra in penis amputation that Dr. Livermore spoke about, there is no question but that you get a far better result if you leave about a centimeter of the cuff of the urethra protruding and then split it a little on each side and turn it back and lightly tack the edges. If you do this, you do not have any stricture of the urethra. It is very much like the results you get with the transplantation of the ureter into the bladder where you poke a hole in the bladder, pull the ureter through, split it and fasten the two split halves back against the bladder with a single suture.

Dr. C. D. Creevy (Closing): Dr. Davis perpetrated a non sequitur because he discussed something which was left out of the paper by design. He implied that we pay no attention to the condition of the patients before doing transurethral resections. I did not refer to the subject, but I want you to know that we do pay attention to the condition of the patient.

I wish to take issue with him about his, shall we say, slavish adherence to the old dicta concerning prostatic surgery. Some of the modern advances which have taken place in recent years, such as the use of antibiotics, transfusions, and developments in anesthesia, to be trite, permit us to do things with safety which, a few years ago, were impossible.

He spoke of sterilizing the urine before a prostatic operation. I do not believe that this can ordinarily be done. I believe that we can now operate with safety in the presence of infected urine. All of us are obliged to do so. I know that it is possible to do a successful plastic at the ureteropelvic junction in the presence of pus in the urine. That, previously, might have imperiled the success of the operation.

We do pay attention to the renal function and to the condition of the patient. We even have a medical consultant in to tell us about the condition of the patient's heart. I do not expect everyone to believe everything about the use of isotonic fluids, but I do submit that their use has accomplished two things: In the first place, the average patient is not sick at all after a transurethral resection; and in the second place, the mortality has been greatly reduced.

Dr. Archie L. Dean (Closing): In my experience, the use of radium has been ineffective in the treatment of metastatic inguinal nodes secondary to carcinoma of the penis. I do not give such treatments and I know of no one in New York who does. The administration of interstitial radiation by implanting radon seeds in each cancerous inguinal node is impracticable. External radiation, whether by means of radium or roentgen rays, is also ineffective because the nodes are the site of radioresistant squamous carcinoma. Usually infection also is present which renders successful radiation still more difficult. Furthermore, the skin of the groins will not tolerate heavy radiation probably because moisture

is present. Finally, the nodes are surrounded by fat which reacts sluggishly to radiation.

In our experience, about 80 per cent of patients with penile cancers have inguinal adenopathy at the time of their first examination. Twenty per cent have no enlarged nodes. Of the 80 per cent, immediate biopsies and protracted periods of observation show that 50 per cent of the nodes are cancerous.

I do not treat inguinal nodes until I know that they are definitely cancerous. The routine local inguinal dissection performed when the penis is amputated is a relatively ineffective operation and there is considerable likelihood that it may be unnecessary. The more efficient radical groin dissection is a serious procedure which usually produces a certain amount of dysfunction of the lower limb and, since the majority of these patients are laborers, the operation should be done only for sufficient cause.

At the time of the penis amputation, with the patient under anesthesia, I do an aspiration biopsy of any suspiciously enlarged node. If evidences of cancer can be found, a radical groin dissection is performed after a few days of active treatment of infection with chemotherapy and antibiotics.

In performing a radical groin dissection, any affected skin, together with all fat, lymph nodes, lymphatics and fascia, is removed from the inguinal region. The inguinal ligament is severed and the abdomen is entered retroperitoneally and the iliac lymphatics are completely removed. When metastases are present in one groin, it is likely that both are affected but, because this operation is tedious and time consuming, usually but one side is operated upon at a time.

As far as the new urethral meatus is concerned, I have found it difficult to leave a length of excess urethra with the assurance that subsequent sloughing will remove only as much urethra as desired and no more.

Performing this precise attachment between the urethra and the skin leaves a well nourished urethral meatus which requires no subsequent dilatation. That appears to be preferable to leaving redundant urethra.

Dr. David M. Davis (Philadelphia, Penna.): I should like to apologize to Dr. Creevy. I know he pays close attention to the integrity of his patients' kidneys, for I have personally observed his work in Minneapolis. When I spoke of that aspect I should have made it clear that I was speaking of other writers and not of Dr. Creevy.

MANAGEMENT OF URETERAL INJURIES

JOHN F. PATTON

From the Department of Surgery, Section on Urology, Washington University School of Medicine and Barnes Hospital, St. Louis, Mo.

Injuries to the ureter in both war and civilian practice are comparatively rare and are less frequently encountered than injury to other levels of the urinary tract. The reports in the literature, however, do not reflect the true incidence since fewer than one hundred war wounds to the ureter have been reported to date and less than one thousand cases of injuries in civil practice. Many remain undetected and others unreported. Apparently stimulated by the last war, there has been an increasing number of articles dealing with the subject and, in general, the principles of management are well defined. These include, though not necessarily in their order of application: 1) early recognition, 2) adequate drainage in the prevention or presence of extravasation, 3) diversion of the urinary stream above the point of injury for protection of the kidney, 4) repair of the defect. These apply regardless of whether the injury is due to a gunshot or shell fragment or the result of some form of surgical trauma. The circumstances of the injury and the causative agent, however, may influence the immediate course of procedure, and each case presents an individual problem. The primary consideration in all instances should be the preservation of the kidney with ultimate restoration of the continuity of the urinary tract to as nearly the normal state as possible, subject of course to first consideration of the individual's life as a whole.

WAR INJURIES

Although the principles involved remain the same, certain aspects of war injuries deserve separate discussion. War injuries of the ureter result from gunshot or shell fragment in which the ureter is either partially or completely severed, and are usually accompanied by more serious injury to the abdominal viscera. Robinson, et al. reported 25 wounds of the ureter and only 2 cases failed to have injury to other organs. In the presence of severe abdominal wounds, injury to the ureter becomes of secondary importance, and as a result they are frequently overlooked. It may be said that in any case of penetrating wound of the abdomen, particularly if the point of entrance is in the flank, or if on abdominal exploration the foreign body is found to penetrate the posterior peritoneum, ureteral injury should be suspected. If the time element is important and prolonging the surgery to determine the existence of a ureteral injury would appear hazardous to the patient's life, the retroperitoneal space should be drained on suspicion. This can be done through a small muscle-splitting incision or even a simple stab wound. While urine from a ruptured ureter draining into the retroperitoneal space may not be of serious consequence, extravasation into the peritoneal cavity may be fatal.

Even if the injury to the ureter is recognized, the condition of the patient

may not permit initial repair of the defect and drainage with exteriorization of the proximal end of the ureter, nephrostomy or ureterostomy, may be necessary as a temporary measure. With adequate drainage and diversion of the urine, one can safely wait until such time as the patient's condition will permit proper investigation and definitive treatment. If initial repair of the ureter is feasible, an end-to-end anastomosis over a splinting catheter, or re-implantation into the bladder is the method of choice. Excessive loss of ureter, necessitating nephrectomy or resort to transplantation procedures, is infrequent.

Ureteral injuries, unfortunately, are usually recognized only after a urinary fistula has developed. Such was the case in 18 of the 25 war injuries reported by Robinson, the fistula developing within the first 10 days. Culp reported 6 cases, only one being recognized early. In Rusche's series of 5 cases, all were recognized late, ranging from 10 days to 10 weeks following injury. In one of these a fistula was not present and the first sign was a mass in the loin with sepsis. In late cases thorough investigation, including excretory urography and retrograde studies, should be carried out to determine the type and location of the injury and the condition of the kidney before deciding upon the necessary corrective measures. The longer the interval between injury and recognition or application of therapy, the more likelihood of the necessity for nephrectomy. Thus early diagnosis is essential. Every effort should be made to preserve renal function, particularly since the combat soldier comprises a young-age group.

CIVILIAN INJURIES

In civilian practice, the most common cause of injury to the ureter is surgical accident, most frequently sustained during surgery in the female pelvis. The age group here is relatively young also, emphasizing again the importance of conservation of the kidney. In a review of 36 cases of injury to the ureter collected from the Barnes Hospital and private practice, over 90 per cent were under 50 years of age, 16 or 44 per cent being in their thirties. In 35 of the cases, injury was due to surgical trauma and in one instance a ureterovaginal fistula developed 3 months after the application of radium for carcinoma of the cervix.

Surgical injuries to the ureter may be unilateral or bilateral and may occur by: 1) ligation, 2) crushing with forceps, 3) distortion from closely approximated sutures, 4) incision or partial division, 5) complete division, 6) resection of a portion of the ureter. Extensive stripping of the intact ureter is probably rarely complicated by any serious effects, as the anastomotic circulation of the ureter protects it from anemic necrosis.

The injury is rarely recognized at the time of the original operation. Such was the case in only one instance in this series. If the injury is discovered, the measures which may be applied will depend on the type and extent of the injury and the patient's ability to withstand prolonged surgery. In the event the ureter has been ligated, deligation and the insertion of a ureteral catheter would appear satisfactory. In the one case referred to previously, I was called in during an abdominal hysterectomy because the posterior wall of the bladder had been opened in separating it from the cervical canal. The trigone was exposed and the ureteral

orifices plainly in view, so catheters were passed to rule out possible ureteral injury. The right ureter was found to be ligated 4 cm. from the bladder and was of approximately 45 minutes' duration. Deligation was carried out, a ureteral catheter left in place and the bladder defect repaired with good end result. The ureter distorted by closely approximated sutures may be handled in a similar way. If the ureter has been partially severed, a splinting catheter should be all that is necessary. If crushed or completely divided, re-anastomosis or transplantation to the bladder seems the preferred choice. Extensive loss of ureter, though rare, may necessitate consideration of such procedures as uretero-intestinal anastomosis, cutaneous ureterostomy or transuretero-ureteral anastomosis as devised by Higgins. The latter has been successfully applied by both Moore and Smith. Ligation of the ureter with the purpose of producing hydronephrotic atrophy of the kidney is to be condemned and is permissible only under the most urgent circumstances. If the condition of the patient does not permit the time required for definitive surgical correction, a temporary nephrostomy or ureterostomy is the safest course.

Unfortunately, the injury is usually not evident until sometime during the postoperative period. Bilateral ligation produces immediate and grave symptoms with anuria and demands prompt intervention by deligation or bilateral nephrostomy. The postoperative course in the presence of unilateral injury is usually a stormy one although there may be no symptoms to direct attention to the kidney. Renal pain may be expected in only approximately 50 per cent of the cases. Oliguria, unusual fever or renal tenderness should make one suspicious and warrants early investigation. A urinary fistula is often the first positive sign and was present in 54 per cent of the 35 cases referred to previously, occurring most frequently between the fourth and eighth day. In one case the fistula developed as late as 21 days.

Attempts at correction of the injury during the early postoperative period may be difficult or even hazardous, and if infection has intervened, would seem contraindicated. Simple deligation over a splinting catheter may be considered feasible in certain instances but, to be successful, must be performed early before the ureter has undergone excessive damage. Moore reports a case of successful bilateral deligation on the third postoperative day. Each case presents an individual problem and it may be said that, in general, temporary nephrostomy reamins the safest course of procedure.

URETERAL ANASTOMOSIS

As stated previously, re-anastomosis of the ureter or re-implantation to the bladder is the method of choice in restoring the continuity of the urinary tract, and likewise they provide a nearer approach to the normal state. Re-anastomosis is generally accepted as the preferred method of repair in dealing with high ureteral injuries and should be equally applicable in most low injuries. The difficulty is usually in isolating the distal segment, but one should be able to accomplish this by careful dissection and the use of a large caliber ureteral catheter inserted from the bladder side to aid in its location. The majority of surgical injuries to

the ureter are found in the lower third. In 15 of the cases reviewed, or 75 per cent of the 20 cases in which the level of injury had been determined, the injury was within 6 cm. of the bladder.

Successful uretero-ureteral anastomosis depends on: 1) careful approximation without tension, 2) preservation of the blood supply of the ureter, 3) adequate splinting and 4) control of infection. Avoiding tension on the suture line is extremely important, and the union should be water-tight. A sufficient number of sutures of fine chromic catgut should be used to accomplish the latter, but no more than is necessary. Leakage of urine at the site of anastomosis increases cicatricial tissue and the posssibility of late stricture formation. Stripping the loose adventitia from around the ureter should be avoided. It is better if the cut ends of the ureter bleed. Polyethylene tubing seems preferable to the ureteral catheter for use as a splint.

Much has been said about the necessity for repeated dilatation following ureteral anastomosis and many urologists perform it as an accepted routine. Although I adhere to the principle, I have often wondered whether or not repeated dilatations of the ureter following a well performed anastomosis were really necessary or actually advisable. In some instances it seems logical to assume that the dilatation may add trauma and give rise to increased fibrosis. If the anastomosis is carefully and accurately performed without tension, the ureter properly splinted and infection controlled, one may rightfully wonder whether the repeated passage of a large caliber ureteral catheter is the deciding factor in a satisfactory end result. Also, if repeated dilatations are necessary in order to keep the ureter open, the anastomosis can hardly be considered as successful, and in such cases progressive hydronephrotic atrophy of the kidney with eventual nephrectomy is the likely course.

I would like to report an early result in a complicated case in which an end-to-end anastomosis of the ureter was performed in a low ureteral injury.

H. G., a woman aged 34, was first seen October 1, 1950. Two weeks before, an abdominal hysterectomy had been performed and on the fourth postoperative day she developed severe right renal pain. Excretory urograms revealed dilatation of the right renal pelvis and ureter. On the sixth day, the patient was cystoscoped and two catheters, Nos. 4 and 5, were passed easily up the right ureter with some relief of pain. The abdomen became increasingly distended however, and on the tenth postoperative day the abdominal wound was reopened and 1000 cc urine were evacuated. The ureteral catheters were found to be coiled up in the abdominal cavity. The abdominal wound was closed around a Pezzer catheter. When she was admitted to the Barnes Hospital 4 days later, the abdominal tube was in place and draining well, the bladder urine was purulent but her general condition was fairly good. Two days later she developed leakage of urine into the vagina through the cervical stump and the abdominal tube ceased to drain and was removed. Excretory urograms revealed a functioning right kidney with only moderate dilatation (fig. 1, *A*). On cystoscopy, a ureteral catheter blocked at 6 cm. up the right ureter but dripped purulent urine (fig. 1, *B*). Culture revealed coliform bacilli and B. pyocyaneous. Because of the gross infection, a nephrostomy was performed to protect the kidney until such time as the field

could be prepared for definitive treatment. A drain was also placed through the cervical canal to improve drainage. On October 25, six weeks after the original operation, a uretero-ureterostomy was performed. The proximal ureter was exposed extraperitoneally and dissected free with ease. The distal segment was bound by dense adhesions but when isolated was found to be of sufficient length to warrant a re-anastomosis. An end-to-end approximation was performed using 0000 chromic catgut and a polyethylene tube of approximately 10F was inserted as a splint and brought out through the urethra. The wound was closed with drainage and a urethral catheter was placed in the bladder alongside the polyethylene tube. The nephrostomy tube was removed at this time. She had an uneventful postoperative course and both the polyethylene tube and the urethral catheter were removed on the eighth postoperative day, at which time

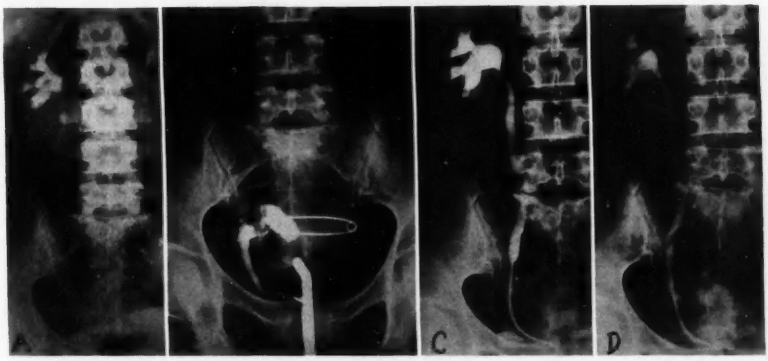

FIG. 1. *A*, preoperative excretory urogram showing degree of right hydronephrosis. *B*, retrograde ureterogram showing point of injury and extravasation of dye. *C*, retrograde ureteropyelogram 13 days postoperative. *D*, retrograde ureteropyelogram after 4½ months showing regression of previous hydronephrosis.

the urine was clear and free of infection. There was no evidence of leakage at the site of anastomosis following removal of the tube. On the thirteenth postoperative day a No. 10 bulb catheter was passed up the right ureter without difficulty and a ureteropyelogram appeared satisfactory (fig. 1, *C*). She was discharged on the following day. A ureteropyelogram after 4½ months shows an essentially normal kidney with evidence of regression of the previous moderate hydronephrosis (fig. 1, *D*). A No. 8 bulb catheter passed up the ureter easily. The final result in this case can only be determined by a later follow-up.

RE-IMPLANTATION TO THE BLADDER

If the distal segment of ureter is not of sufficient length to permit re-anastomosis, re-implantation of the proximal ureter into the bladder is the method of choice. Numerous techniques have been proposed for re-implantation and it is generally agreed that the preferred site is the base or fixed portion of the bladder.

I wish to present a late follow-up of a case previously reported and which to the best of my knowledge is the first instance of re-implantation of the ureter into the bladder through the normal intramural bed.

L. B., a white woman, aged 32, was first seen March 30, 1938 because of a ureterovaginal fistula of 10 months' duration, which followed a hysterectomy. It was possible to catheterize the ureter through the vaginal fistula and retrograde studies revealed a functioning kidney with only moderate hydronephrosis (fig. 2). Operation was performed on April 5, 1938; the ureter was exposed extraperitoneally, followed down to its entrance into the vagina, and was found to be free of any connection to the bladder. The bladder was opened, a small sound passed through the left ureteral orifice and forced through the stricture at 2 cm. The proximal end of the ureter was severed from its attachment to the vagina, a forceps passed through the intramural ureter from the bladder side and the lower end of the proximal ureter was grasped and drawn into the bladder. The

FIG. 2. Preoperative retrograde left ureteropyelogram. Ureter catheterized through vaginal fistula. Mild hydronephrosis.

end of the ureter was split for about 1 cm., the flaps folded back and one suture of chromic catgut was taken through each flap and carried through to the posterior surface of the bladder (fig. 3). A No. 8 ureteral catheter was used as a splint and brought out through the urethra. The bladder was drained by a urethral catheter passed alongside the ureteral catheter. The bladder was closed without suprapubic drainage. The ureteral catheter was removed on the twelfth postoperative day and the urethral catheter on the seventeenth day. Six weeks after operation a cystogram showed no evidence of regurgitation of bladder contents up the ureter (fig. 4, *A*). Six months later cystoscopy showed an essentially normal ureteral orifice which admitted two No. 5 catheters without difficulty, and ureteropyelogram showed an essentially normal pelvis and ureter. A follow-up in 1946, eight and one-half years later, shows a normal pelvis and ureter (fig. 4, *B*) and she had had only one episode of mild urinary tract infection during the interval.

This method reproduces the normal anatomical relation of ureter to bladder

and preserves the function of the ureterovesical valve. It should be applicable in any case in which the proximal segment of ureter is of sufficient length to permit re-implantation to the base of the bladder.

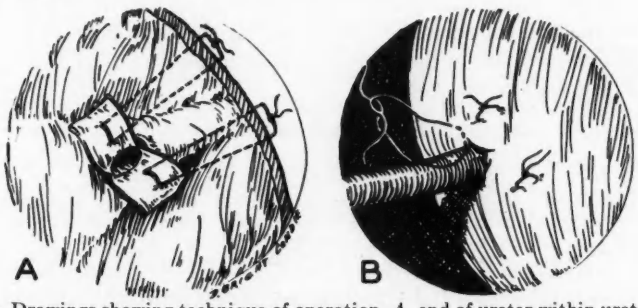

FIG. 3. Drawings showing technique of operation. *A*, end of ureter within ureteral orifice with end split and flaps folded back. One suture through each flap to posterior surface of bladder. *B*, posterior view of bladder. Ends of sutures tied. One traction suture through outer wall of ureter and bladder.

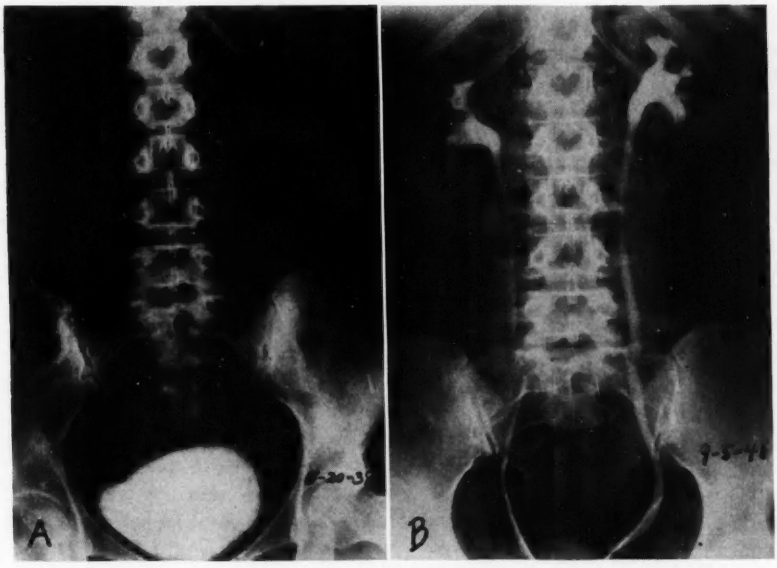

FIG. 4. *A*, cystogram 6 weeks after operation showing no regurgitation up ureter. *B*, bilateral retrograde ureteropyelogram after 8½ years showing essentially normal left pelvis and ureter.

SUMMARY

The importance of early diagnosis in ureteral injuries is emphasized, together with prompt application of appropriate measures to insure preservation of renal function.

Initial repair of the defect is preferable. Early repair is desirable. If not feasible,

temporary nephrostomy is the safest course of procedure. Later repair depends on the condition of the patient, type and extent of the injury and presence of infection. Nephrectomy should be reserved for the irreparably damaged kidney.

Uretero-ureteral anastomosis and re-implantation of the ureter into the bladder are the methods of choice in re-establishing the continuity of the urinary tract. Utilization of the intramural bed for re-implantation of the ureter has been demonstrated as successful.

723 University Club Bldg., St. Louis 3, Mo.

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DISCUSSION

DR. JOHN N. ROBINSON (New York, N. Y.): I have 2 cases of injury to the ureter that I want to tell you about briefly.

The first one is a 47-year-old housewife who was seen in urological consultation following a partial colectomy for carcinoma of the sigmoid, because of urinary drainage from her abdominal wound. The procedure at operation was difficult because the patient was obese and had had a previous hysterectomy which left multiple adhesions. During the process of mobilizing the growth, which was situated at the peritoneal reflexion, severe hemorrhage was encountered. It was necessary to resect the colon above and below the tumor in order to control the bleeding, and when this was finished the patient's condition was so poor that the rectum could not be removed. The rectal pouch was then closed with a whipover suture. An excretory urogram showed marked dilatation of the right ureter with pocketing of dye over the sacrum leading to the diagnosis of ureterovaginal fistula. At cystoscopy the next day a catheter was passed up to the right kidney without obstruction. The catheter was left indwelling for seven days until it fell out. Several attempts were made on different days to reinsert it but without success. One week later a rectal examination done for pain revealed a mass protruding from the top of the rectal pouch. On the following day urine began appearing at frequent intervals from the rectum. Proctoscopic examination confirmed the fact that urine was coming from the upper end of the rectal pouch. This film shows dye in the rectum as well as in the bladder. This excretory urogram taken 1 month later shows normally functioning kidneys. At this time it was impossible to pass a catheter up to the right kidney but the patient was voiding four times a day by rectum and by urethra. Films 5 months later still showed normally functioning kidneys. Another x-ray taken a few days ago, a year after her operation, shows again normal kidneys. The fistula has remained patent and the patient happy.

My second case is a 46-year-old woman who had a carcinoma of the cervix. She was treated first with x-ray (4000 r intravaginally) and then by a Wertheim operation. Preceding this procedure catheters were passed up both kidneys and no injury to the ureter was noted at the time of the operation, but 12 days after it she developed a ureterovaginal fistula with urine coming from the vagina. The excretory urogram showed the fistula between the ureter and the vagina. At the operation to cure the fistula there was no evidence of recurrent carcinoma but very dense adhesions deterred us from performing a re-implantation of the ureter into the bladder. Hence a uretero-ureteral anastomosis was done leaving an indwelling catheter in the left kidney. This x-ray taken 3 weeks after the procedure shows functioning kidneys.

Unfortunately, 2 months later the patient was again admitted to the hospital in uremia. The anastomosis was patent but complete obstruction had developed below the site of our repair. Bilateral nephrostomies were done as life-saving procedures.

Dr. Carl Rusche (Hollywood, Calif.): Dr. Patton's suggested procedure of re-implantation of the ureter into the bladder through the normal intramural bed appears to be an excellent way of treating the ureter when the injury occurs near the bladder.

It is a generally accepted belief among surgeons, gynecologists, and urologists that trauma to the ureters is a fairly common and a serious complication to pelvic surgery.

There are two problems to consider in a review of this interesting subject of injury to the ureter. I would like to stress, by repetition, the apparent indifference in the recording of cases of surgical accidents to the ureter. In a 20-year review of the official disease indexes in the medical record libraries of three private hospitals in the Los Angeles area, I was unable to find a single instance of an injury to the ureter associated with abdominal surgical procedures. However, injuries due to intra-ureteral instrumentation and external violence (gunshot wounds) were always reported. The importance of recording the findings in these surgical injuries is of interest and protection to both the physician and the patient, as frequently there is considerable delay in making a diagnosis and instituting the proper treatment when the hospital chart does not contain the pertinent facts.

The second problem is the medicolegal aspect which is involved when this accident occurs. No reasonable person will argue with the theory of law, which provides that a person who has been injured by the carelessness or ignorance of another person should be compensated for that injury. A physician, in treating his patient, is legally bound to possess and to exercise the degree of care and skill such as is commonly possessed and exercised by other reputable physicians in the same field of practice.

Injury of the ureter may generally be classified as an unpreventable surgical accident and in such a circumstance no liability does or should devolve upon the operating surgeon.

However, the relationship between the physician and patient is one of trust and confidence, requiring the physician to act toward his patient with the utmost good faith at all times. It may reasonably be argued that it is the duty of the physician to inform his patient, or someone on behalf of the patient, as to all the pertinent facts of the case. Thus, the physician has a duty to disclose the occurrence of a surgical accident whether negligently inflicted or otherwise.

I cannot help but feel the malpractice problem would grow less serious if all physicians thoroughly understood their legal obligation to their patients.

Dr. Vincent J. O'Conor (Chicago, Ill.): I would like to support the point which has been made by Dr. Carl Rusche. Injury to the ureter during vaginal and abdominal hysterectomy procedures, or a subsequent vesicovaginal fistula after pelvic surgery should not be brought to light in discussing these complications with the patient, or their relatives, as anything but an unavoidable complication. If we as urologists will not criticize the gynecologist who gets into trouble, we will do both the patient and his family a real service. If they understand that a resultant injury is a part of the hazard of these particular operative procedures, a great deal of good will will be spread from every angle.

During the past 9 years at Wesley Memorial Hospital we have treated 21 patients with ureterovaginal fistulas. Four of these patients had surgery within our own institution, and the other seventeen elsewhere. Two of these patients seen recently developed ureterovaginal fistula spontaneously at a very late date. One patient had an abdominal hysterectomy and radium treatment, with an apparent cure of the body of the uterus 8 years prior to the development of the fistula. The ureter above the fistula was not dilated and a normal kidney was present. A re-implantation of the ureter into the bladder in this case was very successful. There is no evidence of carcinoma in the pelvis, and apparently the patient is cured of the original lesion. Another unusual instance seen during the past year was a patient who had a vaginal hysterectomy followed by radium application to the cervix 6 years before consulting us. Practically 6 years after her radium and surgery, she developed a ureterovaginal fistula, and here again the kidney was not hydronephrotic, and the ureter was normal. Here again, re-implantation of the ureter was successful. These two patients demonstrate that a fistula can occur months, or even years, after the original procedures of surgery and radiation.

I am familiar with Dr. Patton's contribution on attempting to bring the re-implanted ureter through the normal intramural area during re-implantation. Unfortunately, in most of the patients whom I have operated upon the ureter was not long enough to make this procedure possible. Terrence Millin has recently re-emphasized this point in a Correspondence Club letter. I would advise against attempting to do this in any instance where tension would result from bringing the ureter down to the edge of the trigone. It is not worth the effort if a slough or a "pull off" is likely to occur.

I would again like to emphasize the importance of Dr. Patton's paper and suggest that in some slightly different form it be circularized rather widely in several state medical journals, so that most of the gynecologists and general surgeons as well as the general practitioners can read it.

Dr. Edgar Burns (New Orleans, La.): I should like to ask a question purely for information and not in the spirit of criticism. Why do ureteral anastomosis in a patient who has a limited outlook?

Dr. William Niles Wishard, Jr. (Indianapolis, Ind.): There are two questions I should like to ask. Perhaps Dr. O'Conor, who has had a great deal of experience with this subject, or the two essayists can answer.

How is a ureterovaginal fistula produced in the course of a supracervical hysterectomy? The general surgeons tell me that most such fistulas are produced in the course of a total hysterectomy. They do not see how it is possible to produce a ureterovaginal fistula in the course of a supracervical hysterectomy, and we have recently seen one instance of a ureterovaginal fistula so produced. Has anyone any explanation?

My other question is this: How long may it take, in case there has not been a complete transection of the ureter, but a ligation, for a spontaneous resolution of the integrity of that ureter to occur? We recently had a patient who had a bilateral ligation of the ureters at the level of the trigone which was all scrambled up with suture material and the ureters were closed.

We had to solve the problem temporarily by bilateral nephrotomy. On the fiftieth or sixtieth day, I have forgotten which, the left one spontaneously opened. The right one never did and it had to be re-implanted.

Is there any information which can tell me how long it is necessary to wait before you are sure you have to do something to re-establish the channel below?

Dr. J. A. C. Colston (Baltimore, Md.): I should like to emphasize a remark which Dr. O'Conor made. It is very important to take care of these fistulas when they occur. I had a very forcible example of this in a recent case. A woman had been operated on 10 years previously. A hysterectomy was performed and was followed by a vaginal urinary fistula. The attending surgeon hopefully watched this fistula close gradually. There was a decrease in the flow of urine from the vagina over a period of several weeks. Finally, the fistula closed. That meant, of course, that the kidney had been destroyed.

Ten years later this patient came in with hematuria. The pyelogram showed a filling defect typical of carcinoma of the pelvis of her remaining kidney. In this kidney there was a condition which could have been eradicated by nephro-ureterectomy. I exposed the kidney and through a pyelotomy incision destroyed the papillary tumor which was present by electrocoagulation. The patient is well at present but, of course, the tumor will probably recur. If this patient had had her injury corrected at the time it was inflicted, this situation would have been prevented. A nephro-ureterectomy could have been performed and the chances would have been excellent that there would have been complete eradication of the disease.

Dr. John F. Patton (Closing): In answer to Dr. Burns, the majority of the 36 cases mentioned were young and preservation of renal function was important. It was not a matter of doing a palliative procedure in the presence of advanced carcinoma.

It is difficult to say when a ligated ureter may resolve itself or how long one should wait. It would seem to be dependent upon the degree of damage to the kidney and the earlier the repair the better the prospect of preserving renal function. If injury is discovered at the time of initial operation, immediate repair is preferable. Unfortunately, however, they usually are not recognized until some time in the postoperative period. I have seen only one case in which an injury was recognized at the time of the original operation and immediate repair gave a good result.

Early recognition of the injury is all important. In the presence of suspicious signs or symptoms, excretory urograms should be made, followed by exploration with the ureteral catheter. In some instances, such as partial tear, an indwelling ureteral catheter may be all that is necessary, provided you can get one up.

RADIUM THERAPY OF BLADDER CANCER, RETROSPECT AND PROSPECT

B. S. BARRINGER

Radiation therapy of bladder cancer, as generally used today, began in the year 1915, in the old Memorial Hospital. The first cure, Mrs. C. A. G., aged 69, came to the hospital on December 1, 1915. She had a large, somewhat necrotic growth covering the left ureteral orifice. Dr. Ewing pronounced it alveolar cancer, much inflamed, with dilated blood vessels. On January 14, 1916, 100 millicuries of screened radium were placed in her bladder as nearly as possible over the tumor area and left in place eight hours. On February 4, 1916, a cystoscopic examination with Dr. Keyes showed no tumor, and the previously obscured ureter was in plain sight, surrounded by normal mucous membrane. She was cystoscoped last on January 24, 1918. Her bladder was normal. In October 1926, she died suddenly of a heart attack. There had never been any return of her bladder tumor.

This one case encouraged us to believe that radium had unusual and unexplored possibilities in the control of bladder cancers. For the next 25 or more years we devoted ourselves at the Memorial Hospital to this task. The task naturally started with the problem of accurate application of radium to bladder tumors and to the determination of what kind of bladder tumors were permanently cured by radium.

Surface application of screened radium was used until early in 1920. Duane, the physicist at the Memorial, developed the glass seeds of radium and I had made by our mechanic the first cystoscopic needle for implanting these glass seeds into a tumor.

Shortly thereafter, Fialla developed the gold seeds of radon which screened out the irritating beta rays, the chief disadvantage of glass seeds. Since then there has been no change in the radon seeds. These gold seeds were implanted with the same cystoscopic needle.

We then sought to widen the field of the implantation of radon seeds by opening the bladder, cauterizing off any projecting portions of tumor and implanting the seeds directly into the tumor base. We reserved the cystoscopic implantation for smaller tumors of the bladder base and lower lateral walls. We placed no restrictions on the size or extent or induration of the tumors which we tried to control by the suprapubic implantation of radon.

After trial and error we finally determined on seeds of a strength of 2 millicuries as most suitable for our work. In the suprapubic approach these seeds were implanted, one to each square centimeter of tumor base, the seeds extending to the edge of the base. The entire implantation was done at one time.

The cystoscopic implantation was quite different; a fractional one. Only 10 or 12 seeds were used at one time. The patient was re-cystoscoped in a month and if the tumor destruction was incomplete more seeds were implanted. Small tumors, papillary or infiltrating could be completely implanted at one sitting.

If the tumor was larger and we believed it could be destroyed cystoscopically, as many as four or five implantations were done, about a month apart. If the tumor became entirely sloughy with no viable red areas, we considered the tumor destroyed and simply watched it cystoscopically.

By this method most failures were due to not using enough seeds or by attempting to control too large a tumor. Considerable experience was necessary to determine which tumors could be cured cystoscopically, experience and a good deal of intelligent persistence. From a quarter to a third of all tumors that came to us we tried to control in this way. From one of our reports we employed the suprapubic method in 129 cases and the cystoscopic in 44.

FIVE YEAR CONTROLS

In the last report in the *Journal of the American Medical Association* ("Twenty-five years of Radon Treatment of Cancers of the Bladder") we recorded "of 94 cases of papillary cancer, including 7 cases of atypical papilloma 49 or 52 per cent were 5 year cures. Of 127 cases of infiltrating cancer there were 30 or 23.6 per cent 5 year cures." If the two types were combined there were 35.7 per cent 5 year cures. No pure papillomas were included in this series.

There is no question that many of the 127 cases of infiltrating carcinoma were totally beyond control by radium. Someone however, had to do experimental work on these tumors and we did it. Our statistics suffered. We learned however, that the solid infiltrating fixed tumor occupying a third or a half of the bladder very rarely could be cured by radium.

These are the tumors that the present day "total cystectomists" are aiming at and with them rests the burden of proof of the value of total cystectomy.

FUTURE PROSPECT OF RADIUM TREATMENT

At the time when the new Memorial Hospital emerged from the old, both at the Memorial and in the country at large, enthusiasm for the radon treatment of bladder cancers began to wane. This was due in noncancer hospitals to the difficulty in obtaining radon seeds in proper amounts. In these hospitals urologists always had operative instruments at hand, but no radium. Radon treatment was obviously from the very start a method to be used in special cancer hospitals where radon seeds were at hand in any strength and amount. Another reason for this trend away from radium was the perfection of the operation of total cystectomy. There was a glamour in doing this operation which the humdrum implantation of radon did not offer. I think it only fair in comparing these two methods of treatment, radium and total cystectomy, to emphasize the relative simplicity of radium implantation either cystoscopically or suprapubically as compared with the severe and extensive operation of cystectomy with its possible aftermath of ureter orifice stricture and hydronephrosis.

A number of competent urologists who have been developing and advocating the operation of total cystectomy have severely criticized radium results. With no exception, as far as I know, has one of these from personal experience sought to learn the possibilities of radium. No one, however, in comparing the two

methods, can afford to pass over lightly the record of five year controls of bladder cancer quoted in this paper.

In the future, I believe that urologists should swing back to perfecting themselves in the cystoscopic method of applying radium, in fractional doses as outlined above. They can do this wherever they prefer to work simply ordering 10 to 12 seeds of 2 millicuries each for each cystoscopic implantation. They do not have to have unlimited supplies of seeds at hand to draw upon, as is necessary when the suprapubic implantation is indicated for a tumor of perhaps indeterminate size.

If they believe the cystoscopic control is impossible and decide on a purely surgical approach to the problem, let them consider the almost neglected method of Beer and Verne Hunt of wide removal of the tumor where possible and reserve total cystectomy for cases with many small cancers scattered widely over the bladder or in large infiltrating cancers. Both of these in our hands have proved beyond control by radium.

New Canaan, Conn.

RESULTS OF STREPTOMYCIN THERAPY IN URINARY TUBERCULOSIS: A FOUR YEAR REVIEW

R. M. NESBIT AND R. L. THIRLBY

From the Department of Surgery, University of Michigan Medical School, Ann Arbor, Mich.

Antibiotic treatment of tuberculosis has afforded a new hope to countless sufferers from this disease; particularly those persons in whom the disease has spread from the primary focus to involve the skeletal system, the urogenital tract or other areas. Favorable results have been reported from many institutions that have used these new agents. At the present time there is no determinative knowledge regarding the optimal dosage or duration of antibiotic therapy; nor is it yet known whether streptomycin is more effective than dihydrostreptomcyin. Likewise there is at present a lack of knowledge regarding the effectiveness of adjunct chemotherapy with agents such as para-amino-salicylic acid. These and other factors will be determined only after long term observations have been made. The Veterans' Administration program under the direction of Dr. John Barnwell is carrying out a large scale program that is carefully controlled and will go a long way in the final evaluation of various therapeutic regimens. Their patients are almost exclusively young males. Civilian institutions will provide data on other segments of the population and so will be helpful in the eventual assay of methods.

Seventy-three patients have received antibiotic therapy in the University of Michigan Hospital since 1946. The present report is based on 64 of these who have been followed a minimum of 6 months after the completion of the therapeutic regimen.

The employment of antibiotics has not radically changed the method of treating urinary tuberculosis in this clinic. They have been used to augment well established principles of treatment. Sanitorium care during and for 6 to 12 months following antibiotic therapy has been considered to be imperative in the treatment of urinary tuberculosis as in other types of the disease.

All cases are first evaluated by cystoscopy and retrograde pyelography, renal function study; and culture and guinea pig inoculation of the separate kidney as well as bladder urine specimens. Having established the presence or absence of destructive lesions, treatment is begun. If no gross lesions are evident by x-ray a 90 day course of treatment and sanitorium care is given following which another complete evaluation with pyelographic studies is made.

In the event of a small or moderate sized unilateral destructive lesion the patient is started on the antibiotic regimen and re-evaluated after 30 days. If there is no evidence of substantial improvement the affected kidney is removed and the course of antibiotic treatment is completed. Patients having severe renal destruction in one kidney are subjected to nephrectomy soon after the beginning of therapy, then the 90 day course is completed. All patients have complete check-up examinations every 3 months for 1 year; every 6 months thereafter.

Currently, dihydrostreptomycin is being used in the dose of 2.0 gm. each day

for 90 days. This regimen has been used for the past 18 months. Prior to that time the patients received streptomycin in doses varying from 1.0 gm. to 2.0 gm. each day for 40 to 120 days. It became apparent that in the treatment of this disease the higher doses of the antibiotic agent were more effective than smaller doses in bringing about remissions. However, vestibular disturbances occurred in a high incidence of the cases that were treated with the more effective amounts of the drug so it was decided to experiment with dihydrostreptomycin in the hope that daily 2.0 gm. dosage of this agent would be less toxic than streptomycin yet just as effective therapeutically. There were several early reports regarding auditory nerve damage produced by dihydrostreptomycin. These were based upon experiences with patients who received the less purified form of the drug in doses greater than 2.0 gm. per day. The purer dihydrostreptomycin in general use today is reported to cause a lesser incidence of auditory nerve drainage. Final evaluation of the toxic effects of both the antibiotics in question is yet to be determined. It is necessary to carry out both pretherapy audiometric and caloric tests as well as post-therapy tests in determining the toxic effects of these

TABLE 1. *Response of urinary tuberculosis to streptomycin and/or dihydrostreptomycin (all cases)*

	TOTAL	REMISSION
First course	64	37
Second course	20	7
Total		44=70%

agents. Recently, pretherapy audiometric tests on one of our patients revealed her to be totally deaf in one ear although she herself was not aware of any deafness. In our series to date we have observed no significant deafness resulting from dihydrostreptomycin; and the incidence of vestibular disturbance following its administration has been about the same as that resulting from low streptomycin dosage. One of our patients, who lost completely his vestibular sense while being treated 4 years ago for bilateral renal tuberculosis in what then appeared to be its terminal stage, has recently said: "The loss of equilibrium has indeed been a small price to pay for the arrest of a fatal disease." This man has learned extravestibular techniques of balance and is working every day in a useful occupation in one of the professions.

The data regarding the effects of treatment in 64 patients having all types of urinary tract involvement have been summarized and are herewith reported.

Forty-four (70 per cent) of the patients have had remission (table 1) and are still free from clinical evidences of tuberculosis 6 months to 4 years after treatment. Twenty-seven of the 64 patients failed to respond after one course of treatment: 20 of 27 failure cases were given a second course and seven became arrested and are clinically well today. Some of the patients who responded to the second course of treatment had tubercle bacilli which in our laboratories showed in vitro evidence of antibiotic resistance. This observation is by no means unique

to our series for other investigations have observed the same clinico-laboratory paradox. One is again reminded that careful laboratory control, though an essential to good clinical investigation, has inherent fallibility, for bacteria do not always act the same in a living host as they do in the test tube.

Table 2 summarizes the results of treatment in patients having bilateral renal tuberculosis. It will be noted that 13 of the 21 bilateral cases had one kidney removed. Nine of these had previous nephrectomy and suffered from involvement of the remaining kidney. Four patients with bilateral disease had advanced cavitation in one kidney while the other was x-ray negative: they were nephrectomized and treated with antibiotics. Eight of these 13 nephrectomized bilateral cases have remained well since treatment.

TABLE 2. *Bilateral renal tuberculosis*

RENAL STATUS	TOTAL	REMISSION
Previous nephrectomy, normal x-ray	7	5
Previous nephrectomy, abnormal x-ray	2	1
Nephrectomy with treatment	4	2
No previous nephrectomy	8	4
	21	12=58%

TABLE 3. *Unilateral renal tuberculosis*

RENAL STATUS	TOTAL	REMISSION
Normal x-ray	8	7
Abnormal x-ray	6	2
Abnormal x-ray and nephrectomy	15	12
Total	29	21=73%

Eight bilateral cases had antibiotic therapy alone and 4 have had remissions lasting to the present date. Thus, 12 of the 21 bilateral cases (58 per cent) have had a favorable response to treatment.

Table 3 is concerned with 29 cases of unilateral kidney tuberculosis. Fifteen of this group were treated by nephrectomy in conjunction with antibiotic therapy. Nephrectomy in all these cases was selected either because the renal involvement was advanced or else because a lesser extensive lesion failed to demonstrate a satisfactory response during antibiotic treatment. Twelve responded favorably and have remained free from relapse.

Fourteen patients with unilateral disease were treated with antibiotics alone. Six were x-ray positive; two have responded satisfactorily to treatment. Eight unilateral cases that were x-ray negative were treated and only one has been a failure to date. Thus, 21 of 29 patients (73 per cent) with unilateral disease have responded favorably to our modern technique of therapy. It is a significant fact that x-ray negative kidneys have shown a high incidence of remission whereas kidneys with destructive lesions have rarely responded.

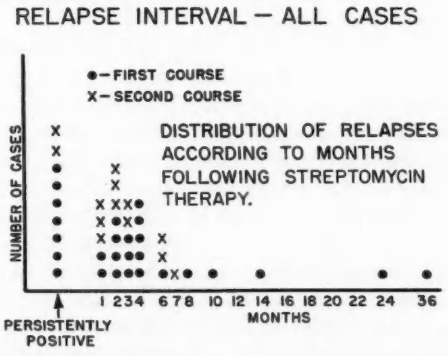
Table 4 relates to 14 cases in which only the bladder was involved with tuberculosis. Seven of these had persisting residual cystitis following nephrectomy; and 7 had tuberculous cystitis yet tubercle bacilli were never found in the urine from either kidney and the pyelograms remained negative. It is likely that the latter group of patients all had renal infection even though our studies failed to demonstrate this point. Eleven of these 14 cases cleared up entirely following antibiotic therapy and have remained well.

TABLE 4. *Residual cystitis and/or genital tuberculosis*

RENAL STATUS	TOTAL	REMISSION
Previous nephrectomy, normal xray	7	6
Normal x-ray—kidney urines negative or not obtained	7	5
Total	14	11=80%

TABLE 5. *Response of individual kidneys*

RENAL STATUS	TOTAL KIDNEYS	REMISSION
No cavitation	25	18=72%
Cavitation present	18	8=44%


RELAPSE INTERVAL — ALL CASES
●—FIRST COURSE
X—SECOND COURSE
DISTRIBUTION OF RELAPSES ACCORDING TO MONTHS FOLLOWING STREPTOMYCIN THERAPY.
NUMBER OF CASES
1 2 3 4 6 7 8 10 12 14 16 18 20 22 24 36
MONTHS
PERSISTENTLY POSITIVE

Opinions have varied regarding the expected response of therapy in kidneys that show x-ray evidence of the disease. Some urologists have held the view that extensive lesions in the kidney cannot be expected to respond; and some have stated the belief that even small caseating lesions which communicate with the pelvis will not heal with antibiotic therapy. In order to gain some information on this point the 43 individual kidneys in the present series of cases have been placed in two groups: those with normal pyelograms and those that show definite pyelographic abnormality, either cavitation or cicatrization. The results of treatment in the two groups are summarized in table 5. Twenty-five x-ray negative tuberculous kidneys were treated and remissions occurred in eighteen (72 per cent). There were 18 tuberculous kidneys with abnormal pyelograms (excluding

hydronephrosis), and 8 of these (44 per cent) responded favorably and have remained in remission. No cases with large caseating lesions showed healing or became tubercle bacilli free. However, some kidneys that showed extensive cicatrization have responded spectacularly.

Among the 64 patients in the series there have been observed a total of 27 failures or relapses following the first course of therapy. Twenty of these received a second course of treatment either because they failed to respond to the first course or else relapsed following a temporary remission. Two of the 20 receiving a second course failed to respond at all and 11 of the remaining 18 have relapsed at some time since the second course of treatment. The rate of these entire 40 instances of relapse or failure have been charted in order to demonstrate the time of occurrence following antibiotic therapy (fig. 1).

In treating a disease that is characterized by its chronicity as well as by its tendency to relapse it is manifestly necessary to reserve judgement until long term observation of cases has been possible. In the present series we have observed that 70 per cent of the cases at present are enjoying freedom from clinical evidences of urinary tract tuberculosis. It must be assumed that some of these will eventually relapse; how many only time will reveal. In this series of cases there are 17 who have been followed for 3 years or more and 7 are well (41 per cent). Thirty-two have been followed 2 years or more and 14 of this group (44 per cent) are in remission. These data do not indicate survival rates alone but rather patients who are both alive and whose urines are free from tubercle bacilli.

It is obvious that antibiotics have a useful and important role in the treatment of urinary tuberculosis; 70 per cent of the present series became bacteria free after treatment. Experience has shown that large dosages of streptomycin or dihydrostreptomycin are more effective than small amounts; and that the regimen should be carried for 90 days or more. It is our belief that these principles should be followed in all cases, and that the employment of a less vigorous regimen is a deplorable compromise in the treatment of this serious disease.

When gross caseation in one kidney is demonstrated by pyelography such a kidney should be removed after a fortnight of preoperative medication, then the antibiotic regimen should be continued for at least 90 days.

Kidneys that are known to be tuberculous yet are x-ray negative or show only minimal destruction should be treated for a month with antibiotics if the lesion be unilateral. If then the affected kidney shows substantial improvement by urinalysis and by x-ray the antibiotic regimen should be carried on to its completion and then another survey can be made. If, after 30 days of treatment, the kidney fails to show marked improvement it should be removed and therapy be continued ito its conclusion.

As a result of our observations on this group of patients, we feel that, although streptomycin is not a panacea for renal tuberculosis, it certainly is a welcome adjunct to the armamentarium used in the treatment of this disease. New hope can be given those so afflicted and the use of streptomycin appears to enhance the patient's chance for an arrest of this otherwise discouraging disease.

INTERSTITIAL CYSTITIS

GEORGE GILBERT SMITH

Interstitial cystitis is today a well-recognized bladder lesion, at least by urologists. The symptoms are characteristic. The bladder capacity is reduced sometimes to as little as 100 cc. When the bladder is distended above a given amount, the patient suffers intolerable pain. If distention is carried above this point, bleeding may occur from fissures which develop in the affected area. Some patients complain of a constant pain which is most frequently referred to the suprapubic area and is sometimes located more to the right or left according to the position of the lesion in the bladder. In a typical case urinalysis shows no pus or bacteria, but there may be a few red blood cells and a very slight trace of albumin.

Although Skene used the term "interstitial cystitis" in the 1887 edition of his *Treatise on Diseases of the Bladder and Urethra in Women*, the condition which he described does not resemble the one with which we are concerned. Nitze, however, in the second edition of his *Lehrbuch der Kystoscopie* (1907) described a typical case of interstitial cystitis and gave the condition the name of "cystitis parenchymatosa." "Panmural cystitis" and "submucous fibrosis" are terms used by later writers to describe this lesion.

PATHOLOGY

On November 13, 1914 Guy Hunner read before the New England Branch of the American Urological Association a paper entitled "A Rare Type of Bladder Ulcer in Women." His description of the cystoscopic appearance and the pathology of this lesion has never been improved upon and is accepted by practically all of those who have since then written on this subject. Hunner wrote:

"Microscopically one finds in the resected portion of the bladder wall a typical picture of chronic, simple ulcer. The epithelial layer is absent at the site of the ulcer and the mucosal layer is occupied by typical, chronic granulation tissue. In some of the specimens this granulation tissue is fairly richly supplied with capillaries, but in most of them there is a preponderance of connective tissue and infiltration of small round cells and leucocytes.

"The epithelial surface in the neighborhood of the ulcer shows multiple layers of the transitional type of cells, the external layers being of the squamous stratified type and in places appearing hornified. Next to the ulcer the epithelial layer may end abruptly with a precipitous edge or there may be seen extending beyond this abrupt edge an attempt at repair in the nature of a single layer of cuboidal cells growing toward the bare surface of the ulcer.

"The mucosal layer in the neighborhood of the ulcer shows an increase in the number and size of the capillaries, varying in the different specimens. The capillaries are often stuffed with leucocytes, as are many of the lymph spaces. There are some enlarged lymph spaces crowded with lymphoid cells and leucocytes, and when these are seen lying beneath the normal epithelium near the ulcer, they at first suggest the picture of tubercle.

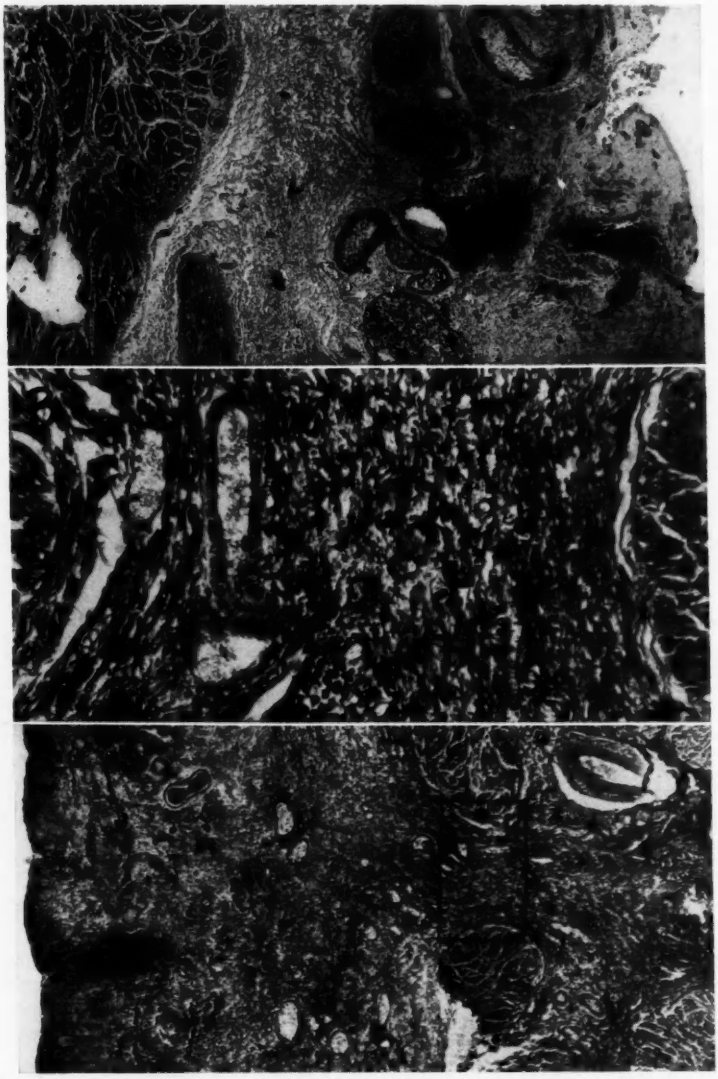


FIG. 1. *A*, low power microphotograph of an area of interstitial cystitis removed from bladder showing eroded mucosa and submucous fibrosis. × 30. *B*, high power microphotograph of lesion shown in *C*. × 150. *C*, low power microphotograph of section removed by subtotal cystectomy showing pathology of interstitial cystitis. × 30.

"There is hyalin degeneration in some areas and in some of the sections the edema causes rarification.

"The muscle coat shows enlarged lymph spaces, and these, as well as some of the blood vessels of the muscle coat, contain many leucocytes. Immediately beneath the ulcer, the muscle in places shows invasion and breaking up by the inflammatory process."

Hunner's communication was the first to describe the symptomatology, the cystoscopic appearance and the pathology of this condition (fig. 1) and to suggest a method of treatment. Since then, the term "Hunner's ulcer" has been in common use.

The extent of the changes in the bladder wall has been emphasized by Nitze, who found the entire thickness of the bladder wall to be involved within a circumscribed area. Kretschmer (1922) gave an excellent description of the pathological findings in an excised portion of the bladder wall and remarked that the enormous thickening of the bladder wall was out of proportion to the size of the ulcer itself. Hand, in studying the changes in the bladder wall, found in a case of interstitial cystitis, was impressed by the extent of nerve involvement as evidenced by edema and leukocytic infiltration about and within the nerve sheaths.

ETIOLOGY

Hunner's paper appeared at a time when metastatic infection from teeth and tonsils was thought to be a factor in many diseases. It was reasonable for him to believe that such foci were the cause of "elusive ulcer," as he called it. There has been evidence to support this theory in the work of Bumpus and Meisser, who in 1921 reported that they had produced lesions in the walls of rabbits' bladders by injecting into the circulation a Streptococcus viridans grown from the infected teeth of patients with interstitial cystitis. Winsbury-White in 1933 described experiments in which India ink injected into the uterine cervix appeared in the lymph spaces of the bladder wall. In my own series of cases with interstitial cystitis there was noted in two instances the occurrence of acute exacerbation of the bladder symptoms following the extraction of infected teeth; one of these patients has been greatly improved since seven infected teeth were removed some fourteen years ago.

Bidgood in 1928 cultured in a banana medium small pieces of bladder wall taken from the involved areas in two cases of interstitial cystitis in which the urine had been sterile; in both instances pure cultures of streptococci were grown.

Kretschmer has reported the results obtained by culturing sections of bladder wall removed from three of his cases. These results were inconclusive; colon bacilli were grown from one, streptococci from another, a few colonies of Staphylococcus albus from the third. A section of bladder wall removed from one of my patients was macerated and cultured; no growth was obtained.

The fact that in the large majority of cases of interstitial cystitis the urine is sterile and usually free of pus does not of itself contradict the theory of metastatic infection in this disease, for the condition is usually a "closed lesion" and infection might well be sealed within the bladder wall.

In spite of the suggestive but not very convincing evidence in favor of the infectious theory, interest in this explanation of the origin of interstitial cystitis has not been maintained. Furniss, in discussing Bidgood's paper, said that in his experience (which was considerable, G. G. S.) the removal of infectious foci had never produced good results in this condition.

An even more weighty argument against the theory that infection is a principal cause of interstitial cystitis is found in the failure of these cases to improve in this era of "miracle drugs." Some patients—and some doctors—have reported improvement after the administration of sulfonamides, but in my experience the good effects have been transitory.

So far as is shown by a search of the literature, there have been only two well-thought-out attempts to discover by experimentation the cause of interstitial cystitis. In 1937 Herbst (R. H.), Baumrucker and German reported an attempt to produce in dogs' bladders lesions comparable to those found in interstitial cystitis. In 15 female dogs adhesions were produced between the bladder and the internal genitalia by scarification; in some the "vessels" of the bladder wall were ligated. Lesions were produced which both cystoscopically and pathologically closely resembled the lesions of interstitial cystitis.

In 1945, Tracy O. Powell reported his "Studies on the Etiology of the Hunner Ulcer." Powell had laid the foundation for these studies by work which he published in *Surgery, Gynecology and Obstetrics* for 1944 on the lymphatics of the female urinary bladder. He found that "the lymphatics of the entire anterior wall of the bladder are drained chiefly by the union of many collectors into a large single trunk, of which there is one descending on each side of the bladder near the obliterated hypogastric vessels and proceeding down along the ureter over the uterine vessels to the primary lymph nodes." Obstruction to the drainage of these main collectors, he postulates, causes a blockage of the flow of lymph, and since there is little or no anastomosis between the lymphatics of the two sides of the bladder, there is a stagnation of lymph and even a retrograde flow in the area affected. Bacteria may be carried to the poorly drained area by this retrograde flow. Among the causes of blockage Powell enumerates the following:

"1) Blockage of a large number of lymph nodes by infection.
   a. Pelvic inflammatory disease now or at some time in the past (specific or nonspecific).
   b. Various types of inflammation as a result of normal or abnormal parturition, abortion, ovarian disease, chronic cervicitis, etc.
   c. Infections in the cul-de-sac, retroperitoneal from perinephritis, etc., peritonitis and proctitis.
   d. Typhoid fever and other diseases that are known to attack lymph nodes.
2) Interruption of lymph circulation by tumors, such as fibroids and other pelvic surgical diseases.
3) Surgical interruption of collectors during pelvic operations.
4) Blockage of anterior horizontal collectors.

a. By infection as a result of cervicitis, giving rise to supravesical fibrosis.
b. By possible pressure from uterus against pubic bone, interrupting rare type of main collector on anterior wall of bladder."

Powell advises that a Frei test be done on all cases; he had several patients in whom the test was positive. Powell says that "the histologic picture in the typical case of elusive ulcer is identical to an hypothetical case of chronic lymphatic edema in that area. Histologic sections of dogs' bladders with partial lymphatic obstruction [produced by the injection of thorotrast into the bladder wall, G. G. S.] were not unlike those in the majority of reported cases of elusive ulcer." Powell says in a paper published in July 1949, that early chronic lymphedema with subsequent fibrosis ultimately involves the parasympathetic nerve filaments, thus producing reflex spasm of the bladder musculature.

Powell's work on the etiology of Hunner ulcer is, in my opinion, most convincing. In one of the few instances in which I resected an area of interstitial cystitis, the edema of the affected area was clearly visible when the external surface of the bladder was exposed. Powell's theory gives a valid reason for the much greater incidence of this condition in females than in males. It explains why interstitial cystitis is most frequent among women of middle age. Bumpus refers to "the noticeable incidence of previous pelvic operations, especially of hysterectomy, among women who suffer from interstitial cystitis."

There is a question as to the existence of factors which predispose to the development of this disease. In my series of 49 women who were so afflicted, in over 50 per cent the symptoms appeared at or about the time of the menopause. It may be of some significance, though I do not know what, that over 50 per cent had never borne children. Kretschmer says that 5 of 13 of his female patients had never been mothers.

Another factor which is of interest has been suggested by John R. Hand. Hand reviewed the histories of 204 women and 19 men who had been under his care and compared their histories with those of an equal number of patients of the same age groups who were under treatment for some other condition. In comparing these two groups, Hand found "a higher incidence of allergies, gallbladder disease, cystoceles, pelvic operations and some types of foci, among the patients with interstitial cystitis than among those in a group selected for comparative study." Hand found also that many of his patients with interstitial cystitis were of a psychoneurotic type; he suggests that interstitial cystitis may be initiated by a neurogenic factor.

Although Hand's work does not lead to definite conclusions as to the exact etiology of this disease, it does give valuable information regarding the secondary factors concerned in its development and chronicity.

TREATMENT

The treatment of interstitial cystitis may be classified as surgical, transurethral and systemic. Perhaps the earliest surgical procedure employed for the relief of this condition was the deliberate formation of a vesicovaginal fistula. Lawson Tait in 1870, suggested making a vesicovaginal fistula as a means of curing

perforating ulcers of the bladder. Skene in 1878 advised this procedure for the relief of what he called "vesico-urethral fissure" and mentioned the names of half a dozen surgeons who had employed "vaginal cystotomy" for bladder drainage and rest. Quinby, in a paper on resection of the presacral nerve, speaks of a woman with interstitial cystitis who in 1929 had been given a vesicovaginal fistula to put the bladder at rest.

Hunner in his early communications advised resection of the affected portion of the bladder wall. For about a decade this operation was the most favored method of treatment, but as Hunner himself said, the incidence of recurrence of the lesion in other portions of the bladder constituted a strong argument against its use. Kretschmer in 1926 reported that in eleven patients whose lesions he had resected there were 50 per cent cured, 10 per cent improved and 40 per cent with recurrences.

Folsom, O'Brien and Caldwell, in 1940, described a much more extensive operation which they hoped would eliminate the possibility of recurrence; this consisted in performing a subtotal cystectomy.

I shall have something to say about this operation in the discussion of my own series.

When other methods of treatment have failed, transplantation of the ureters into the sigmoid has sometimes been done. So far as I can learn, Counseller was the first to do this. In 1937 he reported 5 cases, the earliest of which was operated on in September 1929. Lower in 1939 reported having done this operation. Higgins advises it if other methods of treatment fail to give relief. There is no doubt that diversion of the urine will relieve the symptoms of interstitial cystitis but until the late results of uretero-enterostomy show a much lower incidence of renal failure, one hesitates to employ this measure for a condition which in itself is not dangerous to life and which may be alleviated by persistent treatment involving little or no risk.

As an alternative to uretero-enterostomy Nesbit has suggested anterolateral cordotomy; in 1946 he reported 2 such cases. Although Francis Grant in 1931 reported a case on which in 1923 he had done this operation for bladder pain "probably due to ulcers of the bladder," I have found no other reported cases until Nesbit's report was published. In discussing cordotomy for the relief of bladder pain, David Band says that "post-operative retention of urine is a common feature temporarily observed after this operation, and if as a result of cystalgia and prolonged frequency of micturition the bladder has become contracted, it may be difficult to re-educate the bladder satisfactorily. On the other hand, in the absence of pain, physiotherapy and tidal lavage may with the cooperation of the patient do much to restore a normal bladder function after a successful cordotomy."

The probability that cordotomy will relieve more or less permanently the symptoms caused by interstitial cystitis makes this operation perhaps a better choice than uretero-enterostomy. Further clinical experience will be necessary before the question can be satisfactorily answered.

The first presacral neurectomy for relief of the pain of interstitial cystitis was

done by Pieri in 1926 (Learmonth). In 1932, Learmonth and Braasch reported 24 cases, eight of which were done because of interstitial cystitis. Among these 8, there was no or slight relief in 5, marked relief in 2; one had been done too recently to know the results.

Richer states that the presacral plexus does not convey sensation arising in the bladder wall, but is concerned only with sensations arising in the peritoneal covering of the bladder. Learmonth noted that when the presacral nerve was cut, there occurred dilatation of the vessels of the bladder mucosa; he believed that presacral neurectomy improved the nutrition of the bladder wall in patients with interstitial cystitis. Schroeder (1930) in patients with this lesion excised the presacral nerve and also the lateral sympathetic chains; if necessary he added intrathecal injection of absolute alcohol. His results were "immediately gratifying" but the number of cases was not given.

Scott and Schroeder in 1938 again emphasized the necessity for transecting the lateral sympathetic chains as well as the presacral nerve if the objective is to do away with painful sensations from the fundus of the bladder. Pain and bladder spasm produced by inflammation of the trigone and bladder neck, as occur in vesical tuberculosis, can be relieved by presacral neurectomy alone, but relief of the symptoms of interstitial cystitis usually requires interruption of the lateral sympathetic chains also. The authors report their results in 11 cases, 8 of which had tuberculous cystitis and three had interstitial cystitis. Of these 3, one was greatly improved for at least 1 year, 1 relapsed in 6 months, perhaps because of a marked urinary infection, and in one the symptoms were improved but not entirely relieved.

Both Pieri and Band are of the opinion that in order to interrupt completely the afferent pathways from the bladder, both presacral neurectomy and section of the sympathetic chains at the level of the sacral promontory are necessary.

Much of our knowledge of the neurology of the bladder is due to the researches of the French school. Jaboulay (quoted by Learmonth) in 1899 suggested interruption of the vesical nerves in the treatment of bladder pain. Latarjet, Richer, Rochat and Cotte have published the results of their study of pelvic nerves. French urologists, and Spanish urologists as well, have been more interested than are we in utilizing the knowledge gained from the researches just mentioned. Victor Richer, in 1939, published a paper on the section of the erector nerves of Eckardt, combined with section of the hypogastric nerves, in patients with rebellious cystitis. Darget and Chenilleau and Serrallach Julia have described methods of injecting novocaine into the region of the hypogastric plexuses through a parasacral approach.

Urologists should be aware of the part which neurosurgery can play in the relief of vesical pain, but in a quite inadequate review of this phase of the treatment of interstitial cystitis, I have not found much evidence of clinical benefits. David Band, in a recent summary of the role of neurosurgery in the treatment of vesical pain, says: "In the relief of cystalgia, neurosurgical intervention from the level of the spinal center in the conus medullaris downwards would appear to be inadequate unless the motor innervation of the bladder is to be sacrificed."

Transurethral Methods of Treatment

The transurethral fulguration of bladder tumors by Edwin Beer (1910) probably stimulated the application of this modality in the treatment of Hunner's ulcer. To my knowledge the first reference to the use of the fulgurating electrode in this condition was in the discussion of Hunner's paper in 1914 where it was stated that Arthur Chute had used this method.

Kreutzmann in 1922 published a paper entitled "The Treatment of Hunner's Ulcer of the Bladder by Fulguration" in which he reported a case so treated by him in 1920. Pain was relieved but the bladder capacity continued to be very much reduced (145 cc). In the discussion of this paper Bransford Lewis said he had used fulguration in several cases but found the condition "rebellious." Buerger fulgurated a bleeding ulcer in one patient with cessation of the bleeding.

Frontz in 1928 said that of 26 cases of interstitial cystitis treated at the Brady Urological Institute within the preceding 5 years, fulguration was used in 5. He stated that the method was useful only in superficial lesions and advised resection of the affected portion of the bladder wall if fulguration was not effective. For the past 20 years fulguration has been employed as one of the accepted methods of treatment.

Overdistention of the bladder, usually with the patient under anesthesia, is also generally employed along with fulguration. Bumpus was apparently the first to comment upon the value of this procedure. His article appeared in 1930.

It is not clear to me exactly why fulguration and overdilatation of the bladder relieve the symptoms of interstitial cystitis as completely as they frequently do. When one considers that the lesion often involves the entire thickness of the bladder wall and consists of a dense fibrous layer binding the mucosa to the musculature, why should a superficial destruction of the mucous membrane plus overdistention give so much relief of pain and an increase in bladder capacity sometimes amounting to a hundred per cent?

The relief of pain may be due to destruction of the nerve endings in the ulcerated area; the injection of absolute alcohol into the area of the ulcer probably produces the same effect.

I have not infrequently observed a one hundred per cent or greater increase in bladder capacity in the first few weeks following overdilatation and fulguration. A good part of this increase can be maintained if the bladder is dilated to the point of tolerance at frequent intervals, perhaps once a week. It is difficult for me to believe that the initial overdistention in the anesthetized patient can produce changes in the bladder wall of such type and degree as to bring about so great an improvement so quickly. It seems more probable that the increased distensibility is due to the effect of fulguration upon the ulcer itself and upon the inflamed and oversensitive nerve endings.

The superficial ulceration produced by fulguration heals as a flat, white cicatrix which, like all scars, is poorly supplied with nerve endings. The fact that further areas of redness may develop at the edge of the cicatrix and behave like typical Hunner ulcers while the cicatrix itself remains white, insensitive and firm, appears to support this theory.

The increase in capacity may be due to the absence of pain when the bladder is distended. According to this theory there would be no need for overdistention, yet in some cases repeated and less forcible distention will result in marked improvement. The explanation of the improvement may be that the filling of the bladder several times at each visit acts as massage on the area of lymphatic stasis and stimulates the circulation locally, or that improvement in the local circulation, by reducing edema and leukocytic infiltration, decreases the abnormal sensitivity of the nerves involved.

Other types of local treatment have been tried. Among these are the injection of absolute alcohol into the diseased area with the purpose of destroying the nerves contained therein (Alexander). A method which has been widely used has been the instillation into the bladder of silver nitrate solution in gradually increasing strength until a solution of 1 per cent or of even greater strength has been reached.

Local treatment based upon an entirely different philosophy has consisted of the instillation of soothing oils—mineral oil, cod-liver oil, gomenol, cajandol and undoubtedly many others.

Radiation of the bladder by the roentgen ray and the application of short wave diathermy have been employed.

Overdilatation of the bladder together with fulguration of the areas of redness, especially those which crack and bleed as a result of dilatation, are the most commonly accepted measures employed in interstitial cystitis. Resection of the area of fibrosis would seem to be the most logical method of treatment if it were not for the likelihood that other areas will develop secondarily.

Systemic Methods of Treatment

Attack has been made upon the local lesion by means of substances introduced into the general circulation. Solutions of peptone and of neo-arsphenamine have been given intravenously, potassium iodide, alpha-tocopherol, ipecac and estrogens orally. The sulfonamides have of course been tried as has streptomycin. With all these therapeutic measures, some patients were relieved, temporarily, enough to inspire some urologist to publish the reports of a few patients whose improvement he attributed to this new method. Antibacterial drugs would seem a priori to have little value. The use of drugs such as potassium iodide or possibly cortisone which tend to soften fibrous tissue seems logical.

My experience with interstitial cystitis includes about one hundred patients seen between the years 1914 and 1951. A number of these patients were seen only once or twice; the diagnosis was made but the patients failed to come back for treatment. There were 49 women and 15 men who did return for treatment for a sufficient period of time to enable me to draw some conclusions as to the effectiveness of the measures employed.

The 49 women in this group fall into four classes as follows:

Group 1. Apparently cured, 13 cases. The criteria for including patients in this group are a) freedom from pain which could be caused by the bladder condition, b) ability to hold urine for at least 2 hours, c) a duration of these two criteria for

at least one year. Actually there was only one case in which the duration of "cure" was under two years; this patient died following an operation for gall-bladder disease after having been free of bladder symptoms for 1½ years. Most of the patients listed as "apparently cured" were found to have bladder capacities of at least 300 cc or reported by letter or telephone that they had no urinary symptoms. One woman over whom I had labored faithfully but had not seen for several years, told me when I called her to inquire as to her condition that she was "perfectly well and had been since she had stopped taking fruit juices."

The longest period of freedom from bladder trouble recorded in this group was 13 years. This patient was first seen by me in 1926. She was 46 years old and had had urinary symptoms for about one year. Cystoscopy showed 5 or 6 very red areas which cracked and bled when the bladder was distended to 120 cc. A culture of the urine and a guinea pig inoculation were both negative. She was treated by dilatation and fulguration in the office for three years with temporary relief; it was not until she had thorough fulguration under anesthesia that real progress was made. I have not seen her since 1930 but by telephone I learned that, except for one period of bladder trouble in 1938, she has been entirely free of bladder symptoms (1951).

Group 2. Improved but still under treatment, 14 cases. This group includes patients who have been under treatment for at least 2 years; 8 have been under treatment for at least 5 years. The longest period was 23 years. The patient with this record I now see every few years, the last time in 1950. Her bladder holds 240 cc with discomfort, frequency of urination averages every 2 hours by day and 2 to 3 times at night. Cystoscopy shows the mucosa to be generally congested and the capillaries more dilated than is normal. No areas characteristic of interstitial cystitis are seen. The patient, who is a model of fortitude, says she is free from pain and is "well adjusted" to her urinary frequency.

Six other women have been kept comfortable by dilatation of the bladder every month. One of these kept up this treatment until her death 10 years later. Several others do well under this treatment for months at a time but now and then develop new ulcers which require fulguration.

Group 3. Women who ceased treatment before the final outcome was determined, 18 cases. Fifteen of these patients were improved by treatment varying from a few visits to visits extending over two years. Three did so well that it seems not unlikely that they may have been cured.

Group 4. Women who were not helped by treatment, 4 cases. One was not improved by previous treatment given by Dr. Furniss and four treatments given by me.

One developed an hourglass bladder due to contraction of the scar of the interstitial cystitis. Her ulcers had been fulgurated twice.

One had not improved by 3 years' treatment, in which the silver nitrate method was used.

A fourth became "worse than ever" after resection of a Hunner ulcer; it is probable that the resection was not sufficiently extensive.

From a review of these 49 cases, it appears that fulguration should have been

carried out in some patients in whom it was not done. Those who did best were the patients in whom the fulguration was the most thorough. Of the 13 cases in the "cured" group, only one had no fulguration; she was treated by bladder dilatation with dilute silver nitrate solution. One was cured by resection of the area of fibrosis and remained well for at least 6 years. In another the best response followed two injections of absolute alcohol into the ulcer. She was well $2\frac{1}{2}$ years later.

A patient in whom subtotal cystectomy was done grew a new bladder fundus with a capacity of 240 cc. Seven years after the bladder resection she developed several areas of typical interstitial cystitis. These were fulgurated and she is now quite free from pain.

Ureterosigmoidostomy was done in one of the patients who was not helped by 3 years' treatment of the bladder. This patient died a few months later, probably of carcinoma of the liver.

In 40 per cent of the women, granular urethritis was present as well as a definite interstitial cystitis. The urethritis was diagnosed by endoscopy and was

TABLE 1. *Age at which symptoms began in men*

AGE	NUMBER
30-39	4
40-49	4
50-59	2
60-69	5
Total	15

treated by cauterization, light fulguration and dilatation of the urethra. Pain during urination is strongly suggestive of urethral involvement; it is not due to interstitial cystitis.

In the group of men with interstitial cystitis, there were 15 whose records are sufficiently complete to be of some value. The age at which symptoms first began to trouble these was somewhat greater than in the group of women (table 1).

The symptoms also were somewhat different. There was not the acute pain in the bladder, often localized in the suprapubic area, which was so frequently a cause of complaint in women. Pain in the men occurred only when the bladder was overdistended; the chief complaint was of frequent urination and an overwhelming desire to void when the bladder was filled to its capacity. Three had had transurethral resections of the bladder neck without relief through failure of the urologist to recognize the true cause of the patient's frequency.

Four showed evidence of infection in the urine, either by the presence of pus or by a positive culture. Eight showed neither of these findings. In 3, the presence or absence of infection was not definitely determined. Only 2 had residual urine, one 45 cc, the other 60.

The diagnosis in all cases was made by cystoscopy. In 7 there was a definite Hunner ulcer; another patient showed a ridge of scar indicating a preceding lesion

in the bladder wall. In the majority of cases, the bladder wall was smooth, the mucosa pale. Upon dilatation with the patient under anesthesia, numerous delicate fissures developed over most of the fundus or tiny bleeding points appeared; dilatation of the bladder by a hydraulic pressure of about 3 feet of water (90 cm.) failed to increase the bladder capacity by more than 75 or 100 cc.

The men with interstitial cystitis were treated by bladder dilatation, usually in the office and without anesthesia. In 3, localized areas of interstitial cystitis (Hunner ulcer) were electrocoagulated.

In one patient, a man with unbelievable frequency of urination—60 times in 24 hours—the ureters were transplanted to the sigmoid. The right ureter was transplanted in July 1945, the left in July 1947. Ten months after the second operation the patient died, probably of pyelonephritis.

As to the results obtained in this group of 15 men, 3 were much improved, 3 were moderately improved, and 2 slightly improved. Seven did not follow treatment long enough to give it a fair trial.

DISCUSSION

It is my present belief that cases of interstitial cystitis should be treated by fulguration and dilatation done under general or spinal anesthesia, and should be followed by regular dilatation at least once a month and at times more frequently. The good results obtained in 16 of my 64 cases indicate that interstitial cystitis does not offer an insoluble problem. If the disease continues to be limited to one area and does not yield readily to treatment, I think that wide resection of the affected area should be carried out. The results which followed one of my two resections and a number of those done by Hunner, Hunt, Kretschmer and others leads me to this conclusion.

SUMMARY

The pathology and etiology of interstitial cystitis are discussed.

Methods of treatment are outlined: surgical, transurethral, systemic.

A summary of the results obtained in 49 women and 15 men is given. Thirteen of the women were cured, many of the others were improved. Four women were not materially improved after adequate periods of treatment.

I wish to express my indebtedness to Dr. Wm. A. Meissner for the excellent microphotographs presented herewith.

1101 Beacon St., Brookline 46, Mass.

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DISCUSSION

PRESIDENT GRAVES: Dr. Nesbit has informed me that Dr. Nicholls who is with us today from England has a special interest in tuberculosis of the urinary tract. We shall be happy to have him take part in this discussion.

DR. M. F. NICHOLLS (London, England): I want to thank you for your kindness in letting me share your discussions. My experience is interesting. I am urologist to a large hospital where we have had a good deal of tuberculosis. What impresses me most is the number of cases of urinary tuberculosis which can be found if you are careful and inquisitive enough. I have 300 bone and joint tuberculosis cases under investigation. The more thoroughly and inquisitively we examine them urologically, the higher the percentage is in which we discover tubercle bacilli in the urine.

It is interesting, but it is not quite so important as it sounds. I agree with Dr. Harris that in the vast majority, healing takes place without any real clinical significance of the disease.

I believe that most of these cases are bilateral, and I believe that is of great importance. It has led me to be extremely cautious in the way I approach this disease surgically because one may find tubercle bacilli coming from one kidney on many occasions, and just not have the luck to discover it in the other when that kidney is infected. I am inclined to be more and more conservative in this matter.

Through the kidness of Dr. Nesbit, I had an opportunity to attend his clinic and read his case records. I have nothing to offer in streptomycin experience which can compare with his wonderful results. We have had no dihydrostreptomycin. His dosage already frightened us and already frightened our patients. We have not been able to push the dosage to what I believe is the logical conclusion.

We have found one thing which I think is obvious, and that is that we can divide tuberculosis into two categories: Those in which the primary lesion, which always must be present, has recently been found in the bones or joints, and glands or lungs; and those in which the renal incident comes out of the blue, and in which, in spite of careful study, we can demonstrate no primary lesion.

That second category has done uniformly well. Great caution should be exercised with regard to the first category where there is some other active lesion.

We have, as yet, had no good results from lesions which show any marked changes on pyelography. I am referring to the use of streptomycin. At the same time I would hesitate to say that all such lesions should be eradicated surgically because I think it is important when there is a general disease not to concentrate on the kidneys, but to concentrate on preserving as much functioning renal tissue as possible. Every now and then it may be justifiable and proper to do a partial nephrectomy rather than a total nephrectomy in a case which is confined to one or the other.

DR. JOHN L. EMMETT (Rochester, Minn.): I am sure that interstitial cystitis is the most commonly missed urologic lesion. I should like to comment on two aspects of this disease.

The first is the difficulty of making the diagnosis in men. It is common knowledge that at least 90 per cent of cases are found in women. For this reason we seldom think of the possibility of its occurrence in men. In most cases of interstitial cystitis in men the symptoms are interpreted as vesical irritability from an obstructing prostate and transurethral resection is done. Owing to the vesical distention with irrigating fluid at the time of resection, the patient experiences relief immediately after operation. Within a few months, however, symptoms recur and only after a careful cystoscopic examination is the lesion recognized.

The second point is the protean manifestations of the disease, which can confuse even the most alert and capable diagnostician. I recall one woman who came to the Clinic and registered in the Section on Orthopedics because of severe pain which radiated down her right leg. It seemed to originate in the vagina. She was sure it was caused by a protruded intervertebral disk and asked for an operation to remove the disk. Only after a negative neurologic and orthopedic examination were other lesions considered. Because of a very mild frequency of urination, cystoscopy was performed. A typical Hunner's ulcer was found, which was located on the lower portion of the right lateral wall of the bladder. When it was touched with the beak of the cystoscope, the pain in the vagina and right leg was reproduced. Overdistention of the bladder under anesthesia gave complete relief.

Dr. John K. Ormond (Birmingham, Mich.): I might say, for Dr. Emmett's benefit, that we tried ACTH in one case of interstitial cystitis without any result.

I want to bring something to your attention which may be premature and which may fizzle out entirely. My resident, Philip Fairey, got the idea, after talking to the gastro-intestinal division, that banthine might be used. It is a drug which has been used for gastric and duodenal ulcers with great success. We have tried it out on seven patients, and it seems to be harmless.

In most of the cases, it has been given after the patient has had the bladder dilated, and that throws some doubt on the result. In two cases it was given to patients who had had no dilatation, and they said they were completely relieved of the pain though we found that the bladder capacity was not changed by use of it, and still had urinary frequency. Speak to your gastro-intestinal people about the dosage. I believe it is 50 mg. 4 times a day. It might be well to remember that none of the patients like it at first. They have to get used to it. Some patients cannot take it at all.

Dr. Richard Chute (Boston, Mass.): I have been doing cystoscopies since 1930 in our tumor clinic, and I thought I knew what cancer of the bladder looked like, but on four occasions during the last two years, I found that perhaps I really did not know. Two women had obvious interstitial cystitis. I was sure of it. Two men had been seen by many people and carcinoma was never suspected. When biopsied, all four cases showed carcinoma.

If you have any chronic ulcers which do not heal, even though they do not look like carcinoma, biopsy them, I urge you.

Dr. Reed M. Nesbit (Ann Arbor, Mich.): Since I, at one time, presented a paper on the subject of cordotomy in the treatment of severe interstitial cystitis, I should publicly like to discuss that matter again.

At the time of publication, we advocated its performance only in patients suffering intolerable pain which could not be relieved by any other means. I still advocate that limitation on its use. The patients we reported were the only patients we found occasion to treat by that method.

One very interesting disclosure emanated from the performance of this operation on those five cases. Two of them had recurrence of pain and pain sense. They required a second cordotomy, and one required a third cordotomy; demonstrating for the first time to neurosurgeons that other routes in the spinal cord, or other tracts, could take over the function of carrying somatic pain.

I have another point to make which might have some bearing on the remarks of Dr. Ormond. We studied the effects of presacral neurectomy in a good many cases and reported them many years ago. Following presacral neurectomy, patients are invariably relieved of pain for a few weeks, and then the pain recurs.

If studied immediately following sympathectomy, they are found still to possess normal sensory tracts going to higher centers from their bladders. You can demonstrate that they still have pain sense. Patients relieved of bladder pain by sympathectomy are not relieved because you have cut pain fibers; they are relieved because something else has happened. It may be because you have relieved spasm in their bladders.

Dr. Clyde Deming (New Haven, Conn.): Some years ago someone suggested that we treat Hunner ulcer with cod-liver oil. I put three patients on cod-liver oil and one is still continuing with it. The point I should like to make is this: Every month when the patient came in, I found she still had cod-liver oil in her bladder. In other words, we had a definite interstitial ulcer of the bladder in which the patient carried residual urine. The oil was in the vertex of the bladder and did not cling to the mucous membrane of the bladder.

Since then, in two other cases, I have found that patients will have 30 to 40 cc of residual urine in the bladder even though the capacity is not more than 100 cc. I am wondering whether or not some of these cases do not carry residual urine, and whether or not that, in some way, the residual urine influences the continuation or the prolongation of interstitial ulcer of the bladder.

My second point is with regard to banthine treatment. We have not tried it on interstitial ulcer, but we have been called in as consultants when duodenal ulcer was being treated with banthine resulting in the patient's developing retention of urine. We were not able to find any obstruction.

Dr. John K. Ormond (Birmingham, Mich.): We have also had a similar experience with one case.

Dr. George Gilbert Smith (Closing): I should like to make a few comments on the very kind discussion of my paper.

Learmonth believed that the improvement which sometimes followed presacral neurectomy in patients with interstitial cystitis was due in part to the improvement of the blood supply to the affected portion of the bladder. He based his belief on observations made while he was at the Mayo Clinic. During the course of several presacral neurectomies, Learmonth stimulated the nerve while a cystoscopist watched for changes which might become visible in the bladder

mucosa. It was noted that, following stimulation of the presacral nerve, there was dilatation of the blood vessels of the bladder mucosa.

Apparently, when the pain in the bladder is done away with by anterolateral cordotomy, one can distend the bladder much more freely than before because the nerve endings are not registering and one can really massage the bladder by dilatation, allowing it to dilate and contract.

In my paper I discussed briefly the reasons why dilatation and fulguration help in these cases. It does seem that if the pain in the nerve endings, which is done away with by certain methods, is relieved, one can dilate the bladder much more than is possible while the sensory nerves are still active.

I noted that in the case reported by F. C. Grant on anterolateral cordotomy, he did one side first and the pain continued; then he did the second side, and the pain was relieved. It continued to be relieved for some time.

Dr. Nesbit's observation about the recurrence of pain in those cases is very interesting.

Dr. Chute's remark about carcinoma is very pertinent. I treated a patient for a time for Hunner ulcer. She developed carcinoma in a different part of the bladder with fatal result. Whether the apparent Hunner ulcer was connected with the carcinoma, I do not know.

Dr. Deming spoke of using cod-liver oil and finding oil in the urine one month later. I have often noted that. I attributed it to the fact that the old oil clings to the mucosa and not to the fact that it was evidence of residuum because I check on the residuum of all the women while they are under treatment. I never noticed that any of the people with Hunner ulcer had residuum, but I shall watch it more carefully hereafter.

The point which Dr. Emmett made about the disease in men is very well taken. I had the same idea he had, which is that in the process of doing a transurethral resection, the bladder necessarily is thoroughly dilated; that would give temporarily, at least, a good effect. Several of my male patients have had transurethral resections, but their relief has been only temporary.

END RESULTS FOLLOWING NEPHRECTOMY IN PATIENTS WITH HYPERTENSION

WILLIAM F. BRAASCH

Mayo Clinic, Rochester, Minn.

TESTICULAR TUMORS: SUMMARIZED DATA AND SUGGESTED PLAN OF TREATMENT

WYLAND F. LEADBETTER, J. ROBERT FEELEY AND JOHN S. WHEELER

Tufts College Medical School, New England Center Hospital, Boston, Mass.

Dr. Braasch's paper will be published subsequently in the *Journal of Urology*. The paper by Drs. Leadbetter, Feeley and Wheeler was published in *Urological Survey*, vol. 1, pp. 447–482, 1951.

DISCUSSION

DR. RICHARD CHUTE (Boston, Mass.): I have seen some of the same cases that Dr. Leadbetter has seen, and I certainly feel that in the cases that are not seminoma, surgery deserves a trial. Perhaps I am prejudiced, but I think the thoraco-abdominal incision affords a wonderful exposure, and I brought with me three slides to give you an idea of the kind of exposure you get.

This is a case that turned out to be inoperable. He had so-called "epididymitis" which was drained by his physician some months earlier, and the incision had cut into his tumor and spread that around pretty much. We excised a panel of scrotum and the external inguinal nodes, the internals, the obturator (all of which were positive), and we thought we were doing well until we ran across perfectly inoperable disease, and we had to quit. This shows you a fairly good idea of the exposure you can get.

This slide shows the ureter coming up here. This is the left side. Here is the spermatic cord retracted laterally. Here is the renal vein. We found in this case the aorta completely encased with disease. It was also around the mesenteric vessels. We had plenty of room up under the diaphragm to work.

I have here pictures of a case I did just a week ago. This shows the mass of glands after dissection. This is the right side. This is the right renal vein here, and that is the left renal vein there. It shows how well you can get access to the other side, the left side, from a right-sided approach.

The glands have been laid back in place.

Dr. Leadbetter should be congratulated on his courageous approach to this matter.

DR. JOHN K. ORMOND (Birmingham, Mich.): I should like to know how soon you can consider a patient cured? Perhaps some of you who have had a great

deal of experience with this type of patient can tell me. We have had somewhat less than sixty cases that we followed, and in only two of them have we had late recurrence. They were patients who received no deep x-ray therapy and both recurred in about six years' time. Our other recurrences occurred in the first two or three years after operation.

In kidney tumor, we can expect metastases and recurrence anywhere up to 20 years. I wonder what it is with testicular tumors.

A few years ago, we summed up forty cases. Our results were very good, we thought. Our policy was to take out the testicle, and then in every case, no matter what the pathology showed, to give deep x-ray therapy. In those cases where we could not clinically demonstrate any metastases, we had about 80 per cent cures.

I cannot subscribe to Dr. Leadbetter's idea of not giving deep x-ray therapy. If I had a testicular tumor and I went to a physician who did a radical operation, I would ask to have deep x-ray therapy as well.

Dr. Clyde L. Deming (New Haven, Conn.): Perhaps I can answer Dr. Ormond's question. Recently we have had three cases of testicular tumors recurring. One recurred 22½ years after the original lesion, one 21 years later, and last week we had a case which recurred 18½ years later.

Dr. John K. Ormond (Birmingham, Mich.): Had they had deep x-ray therapy?

Dr. Deming: They had had no x-ray and no resection of the glands.

Dr. Richard Chute (Boston, Mass.): I should like to make one more remark. It was brought to my mind by a question Dr. Culp asked me. Since the primary metastases go via the lymphatics accompanying the spermatic vessels to the region of the renal pedicle, one should go above first and inspect that region rather than go below first and work your way up the cord.

Dr. Wyland F. Leadbetter (Closing): When may patients be considered cured after the removal of a testicular tumor? The majority of deaths occur within the first 2 or 2½ years. If patients live beyond that, without evidence of recurrence, it is fairly safe to assume they may be cured.

THE ROLE OF INFECTION IN NEPHROLITHIASIS

GRAYSON CARROLL AND ROBERT V. BRENNAN

From the Department of Urology, St. Louis University, St. Louis, Mo.

The role of infection in nephrolithiasis may be discussed under the following topics: 1) the role of bacteria in the formation of an original stone, 2) the role of bacteria in recurrence of stone, 3) the effect of bacteria as a secondary invader due to the presence of stone and 4) the suggested treatment of the infection when present.

THE ROLE OF INFECTION IN STONE FORMATION

This phase of the subject will be mentioned only briefly. Many investigators hold to the opinion that bacteria play an important part in original stone formation. Others believe that it plays a very minor part, if any at all. Those who hold

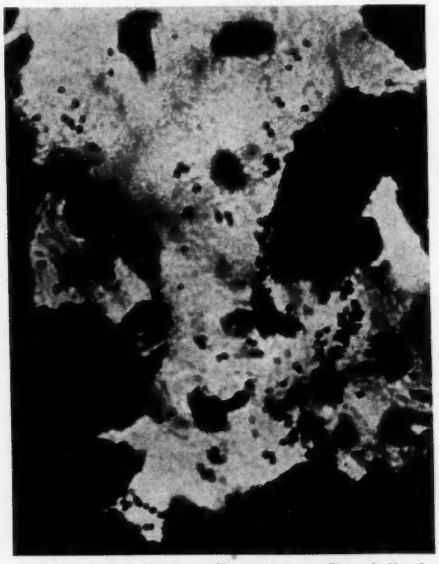

FIG. 1. Bacteria shown adjacent to a Randall plaque

to the former view conceive the mechanism to be a) the initiation of the Randall plaque by the production of damaged or necrotic tissue at the renal papilla by bacteria, b) the bacteria forming the nucleus of the stone formation and c) the disturbance of the colloid and crystalloid balance in the hypertonic urine.

In evidence that infection is the forerunner of the Randall plaque, Edward C. Rosenow, Jr., reports that he found "bacteria adjacent or near to regions of calcification in the renal papilla in 24 of 37 cases in which sections were stained for organisms. Of 24 papillae, not showing plaques, a few bacteria were found in only one case." See figure 1.

Keyser experimentally produced renal calculi by traumatizing the renal papillae and injecting a culture of bacillus proteus. He termed this area as necrobiotic tissue. See figure 2.

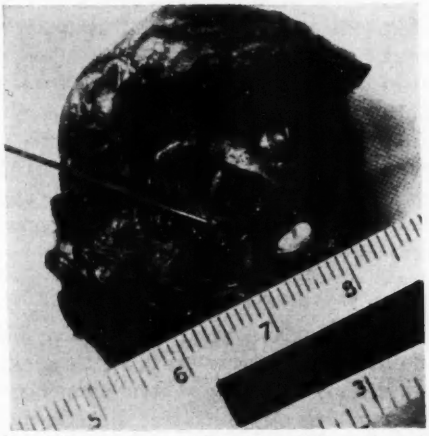

FIG. 2. Stone produced by trauma and infection of B. proteus (rabbit's kidney)

FIG. 3. Staphylococci in center of original amorphous phosphate stone

Herman recites a striking case of a 9 year old boy with osteomyelitis of the tibia, the infecting organism being staphylococci. On admission the urine was normal and 2 months later bilateral stones were found and when removed were found to have staphylococcus as a nucleus.

Hellstrom of Stockholm makes a strong case of the thesis that staphylococci provide a nucleus for stones of amorphous phosphate. He cultivated staphylococci from the center of stones and even in instances where the B. coli was cultured in the urine, staphylococci were found in the organic framework of the stones. All this would testify to the probability that stones may be formed with bacteria as the nucleus. See figure 3.

There is a paucity of information concerning the effect of bacteria on the colloids. Dr. Arthur Butt has recently revived our interest in the colloidal theory. He reported that colloidal activity is increased in the Negro and in the pregnant woman, suggesting this as an explanation of the small percentage of calculi found in these cases. He also stated that hyaluronidase apparently created increased colloidal activity in urine and when administered prevented the formation of encrustations where indwelling catheters were present.

THE ROLE OF BACTERIA IN THE RECURRENCE OF STONES

There is little disagreement concerning the part that infection plays in the recurrence of stone formation. Its occurrence is most commonly due to the urea splitting organism which causes the urea to form ammonia and carbon dioxide. This highly alkaline state changes the soluble monocalcium phosphate to the more insoluble dicalcium phosphate which always occurs in a highly alkaline urine.

We rarely see infection accompanying stones of uric acid, cystine, xanthine and oxalate (Weddellite) variety. Hammarsten experimentally produced calcium oxalate calculi in noninfected urine in rats, and this experiment was reproduced by Edward Prien. An analysis of 100 stones in our clinic revealed of 10 uric acid stones, the urine was noninfected in 8; of the 57 calcium oxalate stones, infection was absent in 40. In contrast to this all of the 24 magnesium ammonium phosphate stones were accompanied with infection. Of the 9 composed of calcium phosphate and carbonate, 7 were accompanied with infection. See table 1.

Suby states that 54 per cent of stone cases in Massachusetts General Hospital are infected and probably all the magnesium ammonium phosphate stones were due to urea splitting organisms.

Charles Higgins found that of 200 recurrent stone cases, 81 per cent were infected. These were large stones. The small noninfected stones were uric acid urates or oxalates.

The impelling conclusion is that the real factors to be considered in the recurrence of stones as far as infection is concerned are stones composed of magnesium ammonium phosphate (struvite) calcium carbonate and calcium phosphate (apatite).

The organism causing recurrence is invariably a urea splitting organism, and any other organism present is the result rather than the cause of recurrence.

It is highly important then to know what organisms have the urea splitting property.

Urea splitting properties have been ascribed to many different organisms. For example, Richard Chute reported that stones of staphylococcus, Pseudomonas

aeruginosa, hemolytic influenza, diptheroids and many strains of Escherichia coli contained urea splitting faculties.

Hellstrom of Stockholm emphasized the importance of Micrococcus as a urea splitting organism.

George Gilbert Smith recognized 2 organisms as the main offenders, Micrococcus and Proteus. He is of the opinion that B. coli are of no great importance.

Albright expressed the opinion that Staphylococcus albus split the urea but that Staphylococcus aureus did not.

To clarify this problem our laboratory made a study of 332 organisms. We were able to demonstrate that practically all of the strains of Proteus vulgaris caused the decomposition of urea in urine.

TABLE 1. *Stone cases with infection*

COMPOSITION	NO.	INFECTED
Calcium oxalate	57	17
Uric acid	10	2
Cystine	0	
Xanthine	0	
Magnesium	24	24
Calcium phosphate—carbonate	3	2
Calcium phosphate	3	2
Calcium carbonate	3	3
Total	100	50

About 50 per cent of the Micrococcus had the faculty of decomposing the urea This property appeared in both the albus and the aureus, hemolytic and non-hemolytic.

Only 5 of the 51 Pseudomonas aeruginosa contained urease, and out of 99 Escherichia coli only 1 had the faculty of splitting urea. See table 2.

It would, therefore, appear that the faculty of decomposing urea in urine is practically always due to the Proteus or the staphylococcus.

The conclusion from these observations is that as far as infection is concerned our problem involves the two organisms, the Proteus and the Micrococcus, and the calculi involved are composed of the magnesium ammonium phosphate, the calcium carbonate and calcium phosphate.

This then simplifies our problem and permits us to concentrate our attack.

The enzyme urease is apparently endogenous. When we filtered urine containing urea splitting organisms through the Seitz filter the filtrate contained no urea splitting properties, thus indicating that the urease is not free in the urine but is dependent upon the presence of the organism itself.

Our first objective is to discover whether a urea splitting organism is present or not.

Hellstrom has invited our attention to the fact that many times in the clinical practice Micrococcus has been noted on the stained smear and yet not grown on the culture. We also have noted this.

Likewise the Proteus may not be properly identified in every instance because of atypical reactions.

Emerson and McIntosh presented to this association a method to avoid overlooking the presence of urea splitting organisms. They utilized a modified Van Slyke method of determining the presence and amount of activity of urease in the urine. The method may be described as follows:

Urease acts on urea in a phosphate buffer solution and the time required for the pH to rise to a definite point is observed. A photocell colorimeter is used to follow the reaction and determine the end point. The amount of enzyme present is inversely proportional to the length of time required for the pH to rise from 6.7 to 7.7 and is expressed in Sumner units. This unit is the amount of urease capable of producing 1 mg. ammonia nitrogen in 5 minutes at 20C under specific conditions.

TABLE 2. *Decomposition of urea by bacteria*

ORGANISM	NO.	UREA +	UREA −
Proteus vulgaris	42	40	2
Staphylococcus pyogenes	39	19	20
Pseudomonas aeruginosa	51	5	46
Escherichia coli	99	1	98
Escherichia intermediate	16	1	15
Aerobacter aerogenes	47	0	47
Paracolon coliforme	6	0	6
Alcaligenes fecalis	14	0	14
Streptococcus fecalis	18	0	18
Total	332	66	266

We have utilized this test with good results and find it to be of value and a reliable method in determining the amount of urease capable of decomposing urea present in the urine. In practical application we have found that the test depends on the urease contained bacteria present, therefore, the specimen must be collected in an aseptic vessel and examined immediately to prevent the increase in the number of bacteria. The presence of a marked amount of pus interferes with the colorimetric readings. A few organisms picked up on culture will give a strong reading bacteriologically whereas the biochemical reading may be very slight. We personally still prefer the bacteriological determination.

TREATMENT

Proteus infections. Having established the presence of a Proteus or staphylococcus infection it is highly important to eliminate it if possible. We will concentrate our report on these organisms.

Aureomycin has proved relatively ineffective with the Proteus. The in vitro tests of 76 organisms showed 7 per cent were inhibited. In vivo study of 12 organisms showed 8 per cent were controlled.

Terramycin also proved ineffective. Of 44 organisms studied 7 per cent were

inhibited and none were controlled in vivo. It would appear that aureomycin and terramycin are not the drugs to use in combating the Proteus infection.

Chloromycetin proved definitely more valuable. Of 78 organisms studied in the laboratory 82 per cent were inhibited. Fifty per cent of patients harboring the Proteus infection were controlled with chloromycetin. The drug would not have proved effective in some of these patients unless very large doses of chloromycetin were given initially; that is, 1 gm. every ½ hour for 3 doses. This created a blood level between 50 and 60 mcg/cc. This permitted an organism which was inhibited in the test tube to be controlled by 16 mcg/cc. No other antibiotic can produce such a high blood level by large doses.

Gantrisin also proves to be an effective agent against the Proteus. Of 53 organisms examined 68 per cent were inhibited. In vivo, 66 per cent were inhibited.

TABLE 3. *Proteus vulgaris* in vitro

	SUSCEPTIBLE	RESISTANT
Streptomycin	49	14
Aureomycin	6	70
Chloromycetin	64	14
Gantrisin	39	14
Terramycin	3	41

TABLE 4. *Staphylococcus pyogenes* (*micrococcus*) in vitro

	SUSCEPTIBLE	RESISTANT
Streptomycin	29	20
Aureomycin	35	5
Chloromycetin	36	3
Gantrisin	11	22
Terramycin	30	18

Streptomycin will control about 77 per cent, but its great tendency to cause the emergence of resistant strains and its awkwardness of administration and toxicity in large doses make it less desirable as a drug of choice. See table 3.

Micrococcal infections. The Micrococcus pyogenes is used here to connote the previously termed staphylococcus according to Bergey's Manual. The Micrococcus pyogenes, as stated before, may be present and not appear on culture. The gram stain should be carefully studied in all persistent alkaline urines for a Micrococcus. Penicillin can no longer be relied on exclusively for therapy. Nichols and Needham found 68 per cent of such infections isolated on the surgical service of the Mayo Clinic penicillin-resistant. Obviously these had received sublethal doses previously. Our study indicates aureomycin and terramycin are highly effective against these penicillin-resistant strains. We recommend the use of large doses of penicillin first and if found ineffective, aureomycin should be given. See table 4.

Arsphenamine, .3 gm. given intravenously every other day for 3 doses, is sometimes dramatic in its effect. The urine from nephrostomy tubes and splint-

ing urethral tubes should be re-examined frequently for alkalinity and staphylococci and Proteus infections and quickly and vigorously treated. Suby's solution and versenate have proved helpful as a continuous irrigating solution and possibly hyaluronidase may be helpful in preventing encrustations.

Sensitivity tests of the infecting organism are essential in the stubborn cases. We have many cases illustrative of the fact that often only one antibiotic came within the inhibition range.

Infection due to the presence of stone. Heretofore our discussion has been confined to the organisms which caused stone formation. Many organisms are present because of the stones. The primary treatment of these infections is surgical drainage and will be discussed by other essayists.

The organisms present as secondary invaders are most commonly Escherichia coli, Pseudomonas aeruginosa, the Aerobacter aerogenes and Streptococcus fecalis.

Escherichia coli are the most common and likewise the most easily controlled by any of our known drugs. Mandelamine or gantrisin is usually effective.

Pseudomonas is the most resistant and as yet there is no nontoxic antibiotic that will inhibit all the strains. Terramycin is probably the drug of choice since we found that of 63 organisms studied, 44 per cent were inhibited. The gantrisin and chloromycetin are notably ineffective.

Aerobacter aerogenes is best treated with terramycin and aureomycin. Streptomycin, chloromycetin and gantrisin are relatively of little value.

Streptococcus fecalis is successfully treated with mandelamine or aureomycin and chloromycetin. Gantrisin is of little value with this organism.

SUMMARY

The role of bacteria in nephrolithiasis is an important one. The organisms involved in the formation or reformation of renal stones are the urea splitting organisms; the Proteus and about 50 per cent of the Micrococcus pyogenes. The stones formed are usually of the struvite or apatite variety; that is, the magnesium ammonium phosphate, the calcium carbonate and the calcium phosphate stones. Infection does not play a major role in the formation of uric acid, urate, xanthine and oxalate stones. Bacteria may play an important role as a secondary invader resulting from obstruction by a stone. These should be controlled when surgical relief is undertaken.

The treatment for the Proteus infection is chloromycetin in large initial doses and gantrisin.

The Micrococcus pyogenes is best treated by penicillin, but there are many penicillin-resistant strains. Terramycin and aureomycin are often effective against these resistant strains.

Drug therapy is suggested for the secondary invaders such as the Pseudomonas aeruginosa, the Aerobacter aerogenes, the Streptococcus fecalis and others.

The careful identification of the infecting organism, the application of sensitivity tests and the drug of choice will appreciably reduce the morbidity and increase the probability of successful treatment of nephrolithiasis.

Humboldt Bldg., St. Louis 3, Mo.

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ETIOLOGY AND PREVENTION OF RENAL CALCULI

CHARLES C. HIGGINS

From the Cleveland Clinic and the Frank E. Bunts Educational Institute, Cleveland, O.

The investigation of the etiologic factors associated with the formation of renal calculi has been stressed by urologists and urologic surgeons interested in the experimental production and dissolution of renal calculi and the clinical aspects of renal lithiasis.

The detection and recognition of the causative factor or factors permit the establishment of a postoperative regimen instituted to minimize the incidence of recurrent stone formation.

In instances in which lesions exist which are amenable to correction by surgical intervention, it may be accomplished at the time the primary calculus is removed from the kidney.

It is generally conceded that no single causative factor is instrumental in the production of all renal calculi; thus in the period of preoperative investigation a comprehensive search is required to ascertain the etiologic factor in the individual patient.

In view of the high incidence of recurrence cited in the past, the surgical removal of the calculus from the kidney must be considered as but one phase in the management of the patient. During the period of preoperative investigation, the following contributing factors merit attention:

VITAMIN A DEFICIENCY

1. Numerous clinical and experimental observations demonstrate the relationship between calculus formation and the absence or a deficiency of certain essentials in the diet. This was especially stressed by Fujimaki[1] and McCarrison.[2] These observers noted "stone areas" or geographic areas in which calculi occurred with unusual frequency in India and China where the people subsist on improperly balanced diets. Since their report additional "stone areas" have been recognized in Turkey, Russia, Egypt, Palestine, England and France, and in other countries.

From the analysis of the diets in these localities, it is evident that the populations subsist on diets which are deficient in certain essentials, or foods poorly balanced in acid and alkaline ash. Several observers have stressed the deficiency of vitamin A in the diets of the peoples in these localities.

2. In the last century, calculus disease was one of childhood in England and France. Joly[3] believes that it is no longer considered a disease of childhood but rather one of adult life. This decrease, in the incidence of stones in children, has been attributed to nutritional and dietary progress. In contrast to this observa-

[1] Fujimaki, Y.: Japan M. World **6:** 29, 1926.

[2] McCarrison, R.: Brit. M. J., **1:** 1009, 1931; also Lancet **1:** 1413, 1931.

[3] Joly, J. S.: Stone and Calculus Disease of the Urinary Organs. St. Louis: C. V. Mosby Co., 1931.

tion, in Russia 55 per cent of calculus disease occurs in children below the age of 15.

3. Geza Illyes[4] stated that the incidence of renal calculi increased enormously since World War I, especially in countries where the inhabitants subsisted on a deficient or poorly balanced diet for an extended period.

In the past we utilized the biophotometer test to determine varying degrees of vitamin A deficiency. It is my belief that this is not an adequate method of determining vitamin A deficiency; the results are not consistent and the antimony trichloride test is the preferable procedure.

In the experimental laboratory I have produced in the white rat: a) stones composed of phosphates with traces of carbonates; b) stones composed of carbonates with traces of phosphates. Oxalate and oxamide calculi in rabbits, uric acid stones in the Dalmatian dog, ammonium magnesium phosphate stones in the dog, calculi composed of the acetyl salts of the sulfonamides in rabbits, and in one patient a cystine renal calculus which was dissolved by employing the alkaline ash diet.

Even if vitamin A deficiency is not demonstrable this diet should be administered postoperatively for its specific healing effect on epithelial structures.

The relationship between foci of infection and calculus formation is subject to question. Rosenow and Meisser[5] demonstrated the specificity of the streptococci in the production of urinary calculi. This work has not been confirmed in other experimental laboratories. They inoculated the pulp of dogs' teeth with streptococci isolated from the urine of patients with calculus disease. The dogs developed calculi and the streptococci were isolated from the urine. I believe foci of infection in the teeth, prostate and cervix should be eradicated.

INFECTION IN THE URINARY TRACT

The relationship between urinary tract infections and calculus formation is evident from a review of the literature. Bugbee[6] in a critical review of 29 patients with renal lithiasis elicited a history of a pre-existing pyelonephrosis in 23 instances.

In a review of 800 consecutive cases of renal lithiasis, I found the culture of the urine to be sterile in 13 per cent.

In 400 consecutive patients observed with recurrent renal calculi, in 288 cases of unilateral stones, the urine was sterile in 216 instances; in 112 cases of bilateral renal calculi the urine was found to be sterile in 20. These studies were made regardless of the size of the calculi.

Harrington[7] in a review of 480 cases of urolithiasis, noted that the culture of the urine was sterile in 26 per cent. Lett[8] in a study of 419 cases of urolithiasis

[4] Illyes, G.: Orvosi hetil, **78:** 889, 1934.

[5] Rosenow, E. C. and Meisser, J. G.: Collect. Papers Mayo Clin. and Found., **13:** 253, 1921.

[6] Bugbee, H. G.: Trans. Am. Assoc. Genito-Urin. Surg., **25:** 121, 1932.

[7] Harrington, H. L.: J. Urol., **44:** 507, 1940.

[8] Lett, H.: Brit. J. Urol., **8:** 205, 1936; also Proc. Roy. Soc. Med., **29:** 1357, 1936.

observed that the culture of the urine was sterile in 18 per cent. Thus while renal infection is not a necessary precursor of stone formation, it is frequently observed.

Complete bacteriologic study is essential including a gram stain of the urinary sediment, culture, test for urea-splitting properties of the offending organism and sensitivity tests.

STASIS

In certain instances renal stasis appears to precede calculus formation. Stasis is conducive to the shifting of the pH of the urine to the alkaline side, and produces a fertile field for bacterial growth.

The presence of stasis may be visualized by excretory urography and, when secured prior to operation, permits correction of the causative factor at the time of surgical intervention. Likewise an initial film and an excretory urogram should be secured before the patient is dismissed from the hospital to determine whether or not stasis has been eliminated and to avoid misrepresentation of false recurrences at a later date.

HYPERPARATHYROIDISM

The relationship between hyperparathyroidism and renal lithiasis has received considerable attention in recent years. In 1934 Barney and Mintz[9] reviewed a series of cases in which the diagnosis of hyperparathyroidism was confirmed by surgical intervention. In 61 per cent of this group calculi were demonstrable in the urinary tract. They stated that hyperparathyroidism is a causative factor in 4 to 5 per cent of the cases. They postulated further that in approximately 70 per cent of cases of hyperparathyroidism calculi are discernible, and in 38 per cent of patients there may be pathologic changes in the bones and urinary tract.

Sangree[10] in a review of 50 cases of renal and unilateral calculi observed one patient with a tumor of the parathyroid gland. Braasch[11] cited an incidence of 0.2 per cent, and I have observed a frequency of 1.8 per cent.

Recently Beard and Goodyear[12] in a review of 150 cases of renal lithiasis stated that hyperparathyroidism was present in 8 per cent of cases.

I believe that hyperparathyroidism is more frequently an etiologic factor than has been presumed in the past. An intensive study is essential to eliminate this possibility. The level of the serum calcium and serum phosphorus and total proteins cannot be evaluated by one determination, but should be repeated. If there is an elevation of the serum calcium and a lowering of the serum phosphorus additional studies are necessary. The patient is hospitalized and after following the Aub diet for 3 days, 24 hour studies are made of calcium excretion in the urine. A Sulkowitch test of the urine detects the gross presence or absence of hypercalcinuria, and roentgenologic survey may reveal bone lesions compatible with

[9] Barney, J. D. and Mintz, E. R.: J. A. M. A., **103:** 741, 1934.
[10] Sangree, H. K.: J. Urol., **59:** 842, 1948.
[11] Braasch, W. F. and Foulds, G. C.: J. Urol., **11:** 525, 1924.
[12] Beard, D. E. and Goodyear, W. E.: J. Urol., **64:** 638, 1950.

the diagnosis of hyperparathyroidism. Routinely, the calcium ion concentration should be determined as it is of primary physiologic and clinical importance. The calcium ion concentration is obviously a resultant of the equilibrium between the total calcium and the total protein. That the investigation of the blood calcium alone does not suffice is evidenced by the fact that fluctuation in the total calcium occurs in response to fluctuations in the concentration of the total proteins in the plasma. Such a fluctuation in the total calcium in the plasma, therefore, is essential in maintaining a normal calcium ion concentration. An increase in the calcium ion concentration in the plasma is strong evidence of hyperfunction of the parathyroid glands.

Hypercalcinuria does not necessarily imply the presence of hyperparathyroidism, as 40 to 60 per cent of patients with renal lithiasis may have hypercalcinuria in the absence of hyperactivity of the parathyroids. The excretion of calcium in the urine is influenced by varying the calcium and phosphorus content of the food, the intake of vitamin D, the renal function and the acidity of the ash in the diet.

CALCIUM PLAQUES

Randall[13] in 1937 described the calcium plaques involving the papilla and stated that they had been observed in the renal papilla in 140 of 609 cases in which postmortem studies were made. In this series of 49, renal papilla with adherent stones were observed.

Vermooten[14] in 1941 in a study of 1060 pairs of kidneys in South Africa stated that in only 88 pairs were calcium plaques observed. Kjolhede and Larsen[15] did not consider that Randall's papillary lesions were new pathologic entities.

Domanski[16] in the experimental production of calcium oxalate calculi in albino rats reproduced the papillary lesions and the calculi were either attached to the tip of the papilla or were loose in the renal pelvis. The incidence of stone formation was highest in the group of rats having a diminished intake of vitamin A.

NEPHROCALCINOSIS

The relationship between nephrocalcinosis and renal calculi is evident by the clinical observation that the first symptom of the disease may be an attack of colic with or without the passage of the calculus. In addition to the characteristic roentgenographic findings of clusters of calcific deposits in the renal pyramids, calculi may be observed in a calyx or the renal pelvis.

The disease was described by Butler, Wilson and Farber[17] in 1936. Since that time additional cases have been reported by Albright,[18] Engel[19] and others.

A diagnosis is established by the typical x-ray findings, acidosis, hyperchloremia, a negative calcium balance, and hypercalcinuria.

[13] Randall, A.: Surg., Gynec. and Obst., **64:** 201, 1937.
[14] Vermooten, V.: J. A. M. A., **109:** 857, 1937.
[15] Kjolhede, K. T. and Larsen, H. K.: J. Urol., **47:** 45, 1942.
[16] Domanski, T. J.: Am. J. Clin. Path., **20:** 707, 1950.
[17] Butler, A. M., Wilson, J. L. and Farber, S.: J. Pediat., **8:** 489, 1936.
[18] Albright, F. and others: Bull. Johns Hopkins Hosp., **66:** 7, 1940.
[19] Engel, W. J.: J. A. M. A., **145:** 288, 1951.

It is Albright's theory that nephrocalcinosis is the result of damage and dysfunction chiefly of the distal convoluted tubules.

METABOLIC DISEASES

Various metabolic diseases may be associated with an excessive excretion of crystalloids in the urine. The following merit investigation:

Gout. Gout is a metabolic disease in which excessive amounts of crystalloids may be present in the urine. The patient may experience repeated attacks of colic due to the passage of a stone or showers of uric acid crystals. The presence of uric acid crystals may be detected in the urine. A normal person excretes 0.3 gm. to 1.2 gm. of uric acid daily; the amount is obviously influenced by diet. It is of interest to note that there may be an elevation of the blood uric acid, and uric acid calculi in the urinary tract, while the patient exhibits no clinical symptoms of gout.

Cystinuria. Cystinuria is a familial disease stated to be caused by the derangement of intermediate protein metabolism. Normally cystine is oxidized, and the sulfur is excreted as a sulfate. In cystinuric patients the cystine is not oxidized to sulfate and the metabolism of the cystine conversion to taurine is undisturbed. It is estimated that 2.5 per cent of patients with cystinuria develop calculi.

Seeger and Kearns[20] in 1925 collected 181 cases of cystinuria from the literature and in 124 instances calculus disease were noted.

The cystine may be found in the urine partly in solution, and also in crystalline deposit.

In instances in which a family history of calculus is elicited, the urine should be tested for cystine, and microscopic study for crystals is advisable.

Oxaluria. Approximately 12 to 30 mg. of oxalic acid which has an exogenous and endogenous source is excreted in the urine daily. Examination of the urine for crystals should be a routine procedure.

Davis, Klingberg and Stowell[21] cited a case of a boy 3 years of age with nephrocalcinosis, nephrolithiasis and calcium oxalate crystals in the kidneys and bones. They suggested this might be due to a defect in the calcium or oxalate metabolism in the patient.

Xanthinuria. In 1934 Kretschmer[22] collected from the literature a series of 15 xanthine calculi cases and added an additional one. We have observed 5 patients with xanthine renal calculi. Uric acid is the most important purine in the urine but 30 to 50 mg. of purine bases, xanthine, hypoxanthine, guanine and adenine are present also.

Phosphaturia. Phosphaturia may be of three types: 1) temporary phosphaturia, induced by partaking of foods with a high alkaline ash or medication; 2) permanent infected phosphaturia due to the presence of urea splitting organisms; 3) permanent noninfected phosphaturia, the cause of which is obscure.

[20] Seeger, S. J. and Kearns, W. M.: J. A. M. A., **85:** 4, 1925.
[21] Davis, J. S., Klingberg, W. G. and Stowell, R. D.: J. Pediat., **36:** 323, 1950.
[22] Kretschmer, H. L.: J. Urol., **38:** 183, 1937.

Thus, it is evident that many factors may be associated with calculus formation. Unless a comprehensive investigation is pursued, and corrective measures instituted, the incidence of recurrent stone formation will remain relatively high. Elimination or correction of the causative factors will be accompanied by a reduction in the morbidity of this disease.

Several procedures may be employed to minimize the incidence of recurrent calculus formation:

1) Maintenance of a large fluid intake (distilled water) and output for 1 year.
2) Elimination of foci of infection.
3) Eradication of infection in the urinary tract.
4) Correction of stasis.
5) Correction of metabolic diseases.
6) Exploration of parathyroid glands in the event that a diagnosis of hyperparathyroidism is established.
7) Additional vitamin A.
8) Chemical analysis of the calculus.
9) Dietary management.
10) Basaljel or estrogen therapy.
11) Treatment of nephrocalcinosis.
    a) Reduce the hyperchloremia.
    b) Correct the acidosis.
    c) Correct the negative calcium balance.

The dietary routine to be advocated is governed by the chemical constituents of the calculus, optical crystallographic or petrologic study, the pH of the urine from the kidney which harbored the calculus, the crystals observed in the urine, and the blood chemistry findings.

The purpose of the diet is to shift the pH of the urine to a point at which the crystalloids, which were constituents of the primary calculi, are maintained in complete solution.

Thus by maintaining the salts in complete solution, the precipitation and formation of accumulations of crystalloids are prevented, thereby eliminating a requisite essential for the formation of renal calculi. Scott has stated that, in most patients with urinary calculi, stone formation is limited to a specific type. When acid stones are formed, usually, an alkaline ash diet will not cause formation of alkaline stones, and vice versa.

In patients in whom the calculi were composed of phosphates, carbonates, or a combination of the two, the high vitamin A acid ash diet is recommended. By maintaining the pH of the urine between 5.2 and 5.4 the phosphates and carbonates are sustained in complete solution, thus eliminating from the urine crystals and sediments which precipitate in alkaline urine. I prefer to determine the pH of the urine in each individual case to ascertain the point at which the salts are maintained in complete solution, as some degree of variation may occur.

For uric acid, cystine and xanthine calculi, the high vitamin A, alkaline ash, low purine diet is advocated. The pH of the urine is shifted by modifying the constituents of the diet, to a point where these salts are not precipitated in the

urine and, at the same time, the alkaline salts are maintained in complete solution. Foods with a high purine content are restricted to minimize the amount of uric acid and urates available to be precipitated in the urine.

When the stone is composed of oxalates, foods with a high oxalic acid content are restricted. The oxalates are precipitated in a wide range of urinary reaction; the pH of the urine may be acid or alkaline. To increase the solubility of the calcium salts, it is advisable to maintain the pH of the urine slightly on the acid side. It is obvious that various combinations of the diet may be required, and this is determined by the chemical constituents of the stone.

This same dietary routine is instituted in the group of patients for whom the diet is prescribed in an attempt to produce dissolution by dietary means. The diet is not applicable for the dissolution of oxalate calculi, inasmuch as oxalates precipitate in urine, the reaction of which is acid or alkaline.

I again reiterate that the role of the diet is only for those patients in whom the pH of the urine may be controlled by dietary means; this constitutes the majority.

It does not suffice to merely prescribe the diet; the patient is required to make daily pH determinations of the urine (which takes only a few moments) and present them to the physician at monthly intervals. In instances in which the pH of the urine is not maintained at the desired level, further dietary adjustment is essential.

There are instances in which the pH of the urine cannot be controlled by dietary means. Usually this occurs in the presence of a urea splitting infection in the urinary tract which cannot be eradicated by the various chemotherapeutic agents available at the present time. Under these conditions the calculi are usually phosphatic in type or composed of phosphates and carbonates.

The role of aluminum gel in this group cannot be overstressed. The principle involved in aluminum gel therapy rests on the fact that the aluminum gel in passing through the gastro-intestinal tract unites with the phosphorus to form insoluble aluminum phosphate which is excreted as such from the bowel. This minimizes the resorption of phosphates from the gastro-intestinal tract, reduces the serum phosphorus, and favors a more complete tubular resorption of phosphatic ions; thus a reduction in urinary phosphate excretion occurs. In reality the phosphates, instead of being excreted in the urine, are now being eliminated in the stool.

The extent of this reaction is determined by the intake of phosphorus and the type and dosage of the aluminum gel prescribed. A normal person, on an average diet, excretes approximately 1 gm. of urinary phosphorus daily. The dosage of the aluminum gel is determined by study of the urinary phosphorus excretion which can readily be reduced to 200–300 mg. per 24 hours.

One other type of therapy may prove to be of value but, while I have used this in experimental work, insufficient data are available to recommend it generally. This consists of the use of estrogens.

The rationale for the use of estrogenic hormones rests on the concept that citric acid in the urine is not a waste product but a useful constituent by virtue

of its capacity to enhance the solubility of calcium, and also on the ability of estrogenic hormones to increase the excretion of citric acid and to reduce that of calcium. At the present time I have used this type of therapy only for those patients having had hysterectomies.

Thus the management of the patient with renal lithiasis is a complex problem of which surgery constitutes but one phase. The fields of chemistry, bacteriology, endocrinology, dietetics and others are involved. Failure to recognize and eradicate the etiologic factors will be followed by a high incidence of recurrent calculus formation. The efficacy of the dietary regimen is determined by the rigidity of its enforcement.

In conclusion, familiarity with all phases of calculus disease, close adherence to the known concepts of stone formation, and the utilization of procedures to minimize recurrent lithiasis, will be attended by a pronounced reduction in the morbidity of calculus disease.

URINARY CALCULI ASSOCIATED WITH NEPHROCALCINOSIS

WILLIAM J. ENGEL

From the Cleveland Clinic and the Frank E. Bunts Educational Institute, Cleveland, O.

The formation of urinary calculi frequently accompanies or follows abnormal renal calcification of the type described as nephrocalcinosis. In an earlier review of 7 cases of nephrocalcinosis, 5 were reported as having stones.[1] In the past year 5 additional cases have come to my attention and all were associated with calculus formation.

In the earlier report all cases presented diffuse bilateral calcifications which were demonstrated by roentgen examination. However, observation of subsequent cases indicates that the disease may be unilateral or even segmental, involving only a portion of a kidney.

In using the term nephrocalcinosis it should be emphasized that it implies no uniform etiology. In a recent review of the subject Vaughan, Sosman, and Kinney[2] point out that abnormal calcification may result from 1) abnormally high concentrations of calcium or phosphorus in the blood with resulting precipitation of calcium phosphate in normal tissue or 2) local tissue damage with precipitation of calcium in the presence of normal blood levels. The former condition is exemplified clinically by cases of hyperparathyroidism. The experimental production of renal calculi by excess feeding experiments, the "hyperexcretion stones" referred to by Keyser, appear also to belong in this category.

The second classification may include a wide variety of conditions, in fact, any condition associated with renal cellular damage. Infections, bacterial toxins, and many chemical agents are known to damage renal cells and therefore may initiate tissue injury followed by calcification. Among the chemical agents, the sulfonamides are apparently causative in many cases as shown by evidence presented previously.[1–3]

Vaughan, Sosman, and Kinney[2] also call attention to the fact that abnormal calcification is more likely to occur where pronounced changes appear in the pH of the media or where there is an increased concentration of phosphatase. Thus the renal tubules with cells high in phosphatase and where there are marked changes in the pH of the media prove an ideal location for calcification.

Many of the cases of nephrocalcinosis have been associated with hyperchloremic acidosis. Albright[4] and his co-workers believed this was due to disease of the distal convoluted tubules, the systemic acidosis having occurred because the kidney was unable to produce ammonia and to excrete acids. The shortage

[1] ENGEL, W. J.: J.A.M.A., **145:** 288, 1951.
[2] VAUGHAN, J. H., SOSMAN, M. C. AND KINNEY, T. D.: Am. J. Roentgenol. and Rad. Therapy, **58:** 33, 1947.
[3] GREENSPAN, E. M.: Arch. Int. Med., **83:** 271, 1949.
[4] ALBRIGHT, F., CONSOLAZIO, W. V., COOMBS, F. S., SULKOWITCH, H. W. AND TALBOTT, J. H.: Bull. Johns Hopkins Hosp., **66:** 7, 1940.
ALBRIGHT, F. AND REIFENSTEIN, E. C., JR.: The Parathyroid Glands and Metabolic Bone Disease: Selected Studies. Baltimore: Wilkins & Wilkins Co., 1948.

of base by which acids are excreted results in an increased loss of calcium in the urine to act as base. This condition can create a local metabolic state favorable for calcification of damaged renal cells.

More recently Latner and Burnard[5] studied 6 cases of hyperchloremic renal acidosis in children. Their investigations indicated that the kidneys were able to secrete free acid and to produce ammonia. They concluded that failure of absorption of bicarbonate in the proximal tubules was the primary cause of difficulty and that calcifications and other changes observed in the distal and collecting tubules result from the hypercalcinuria and chronic acidosis. It is interesting to note that only one of their cases presented the typical x-ray findings of clustered renal calcifications while another with negative x-ray findings disclosed well-marked nephrocalcinosis at autopsy.

Not all cases of nephrocalcinosis are associated with elevated blood chloride and low CO_2. Boyd and Stearns (cited by Vaughan)[2] reported a case of chronic acidosis and rickets which they believed due to renal tubular inability to produce an acid urine; however no renal calcification could be demonstrated. This is additional evidence for the opinion that the renal calcification is secondary and is the result or subsequent development of the renal tubular damage from whatever cause.

Considerable experimental work has shown that calcification follows toxic tubular damage. Randall[6] demonstrated that the kidney excretes and concentrates bacterial toxins. Injections of a streptococcus toxin caused localized epithelial damage most pronounced in the collecting tubules and tip of the renal papilla. Injections of a chemical toxin—uranyl acetate—produced necrosis of the convoluted tubules with extensive deposits of calcium salts in the necrotic epithelium. Keyser[7] obtained a B. pyocyaneus culture from a patient with bilateral renal stones. Injection of this organism killed rabbits by producing hemorrhagic tubular nephritis while a diluted filtrate produced an aseptic nephritis with terminal tubular calcifications. In two instances small microliths were found which were composed of calcium carbonate and phosphate. The calcifications were at the tips of the pyramids. Keyser also produced stones by artificially traumatizing the renal pyramids and inoculating the area with urea-splitting Proteus organisms. It is to be noted that both of the last mentioned experimental workers observed the chief changes in the collecting tubules and renal papilla although calcification also occurred in the convoluted tubules. This finding coincides with the histologic examination of human kidneys where nephrocalcinosis has been present.

Having considered the theoretical and experimental background let us explore the clinical features of this problem. My interest in this condition was aroused by the case of a 4 months' old baby boy included as case 1 in the earlier report.[1] He had an acute toxic nephritis with oliguria, hematuria and azotemia (urea 84 mg. per cent). The history strongly indicated a reaction to sulfonamide

[5] Latner, A. L. and Burnard, E. D.: Quart. J. Med. **19:** 285, 1950.
[6] Randall, A.: Internat. Abstr. Surg. **71:** 209, 1940; in Surg. Gynec. & Obst., 1940. Randall, A.: J. Urol., **44:** 580, 1940.
[7] Keyser, L. D.: South Med. J., **38:** 709, 1945.

medication. As the child improved, there was return of normal glomerular function and normal blood urea. Evidence of tubular damage persisted, however. He had a mild acidosis with elevated blood chloride, polydipsia, polyuria and hyposthenuria. A subsequent roentgenogram of the kidneys revealed bilateral diffuse, minute, faintly visible calcification which occurred in clusters corresponding with the renal lobules. He was observed periodically for the following 19 months, during which time the renal calcifications became progressively more pronounced and he began passing small calculi (fig. 1, *A*). During this time the child appeared to develop normally and there was no radiologic evidence of bone change.

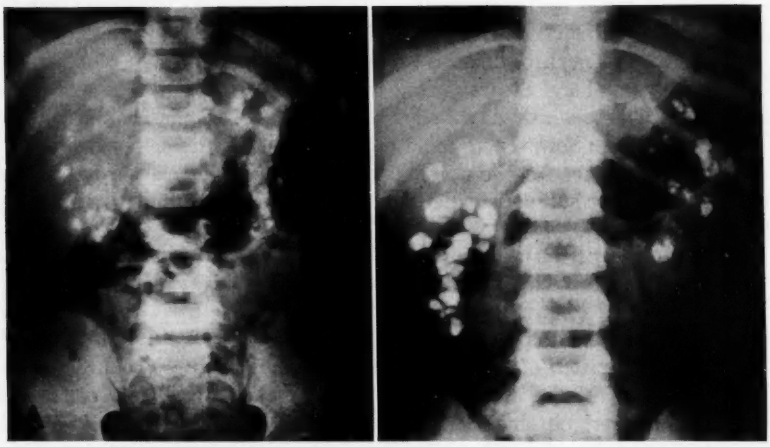

FIG. 1. *A*, Plain roentgenogram showing multiple clustered calcifications occurring in child of 19 months after acute toxic nephritis. *B*, plain roentgenogram of 2½ year old brother of patient shown in *A*. Note bilateral nephrocalcinosis and multiple calculi in right renal pelvis.

Shortly after the discovery of the nephrocalcinosis in this child the mother related that a son aged 2½ had been passing stones. At my request the boy was examined and extensive bilateral nephrocalcinosis was found with multiple stones in the right renal pelvis (fig. 1, *B*). He also had polydipsia and polyuria with enuresis and the specific gravity of the urine was never observed to be above 1.012 (early morning specimen). He had developed normally and there was no radiologic evidence of rickets. The history in this case indicated renal injury, probably the result of an early treatment with sulfa drugs. At that time the mother had noted "red urine". This was not a familial disease as indicated by the fact that roentgen examination of the kidneys of all other members of the family revealed no suggestive calcifications.

The relationship between the nephrocalcinosis and the development of calculi in these children appeared to occur in the following sequence: toxic renal injury followed by calcification in the tubules and papilla, progressing to stones in the renal pelvis. As previously stated, 5 of the 7 patients who formed the basis of

the earlier report had passed stones and the sequence of events followed a similar pattern.

Interest in this subject brought other cases to our attention and we discovered previous cases seen at the clinic in which the true nature of the problem had not been recognized. In this connection I think it pertinent and instructive to relate that, on the basis of the radiologic findings, 2 of the cases had been mistakenly diagnosed as renal tuberculosis, an understandable error since the type of calcification may in some cases be almost identical.

A summary of the histories of the additional cases of nephrocalcinosis associated with calculi follows:

Case 1. A man aged 47 was first seen at the Clinic in January 1944, complaining of pain in the back and sciatica. He had been ill for about 3 months and,

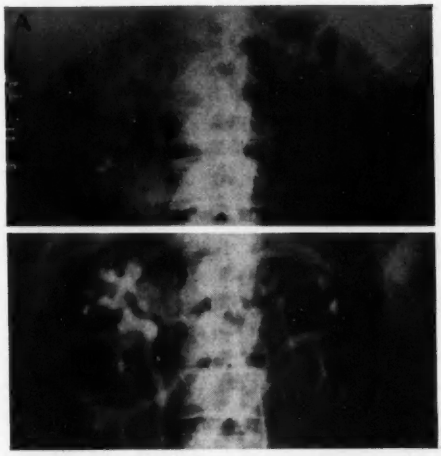

FIG. 2. *A*, plain roentgenogram and *B*, excretory urogram of case 1 made soon after original visit. Note very fine renal calcifications occurring distal to calyces.

associated with the discomfort in the back, had experienced pain in the hip. Previous to the development of the present symptoms he had had an otitis media followed by a draining ear. The most significant finding on examination was the presence of an indurated tender mass in the right flank. The white blood count at that time was 26,850, with 3,870,000 red blood cells and 74 per cent hemoglobin. The blood urea was 96 mg. per cent, which on recheck examination three days later, was 81 mg. per cent. The tender mass in the right flank was thought to be an abscess, probably a psoas abscess. Plain film of the abdomen showed some obliteration of the right psoas shadow. There were multiple small pinpoint-sized calcifications diffusely scattered through both kidney areas (fig. 2). The possibility of renal tuberculosis was considered, but tubercle bacilli could not be demonstrated on repeated examinations of the urine.

On February 10, incision and drainage of a large abscess in the right flank was performed. Smears and culture of the pus were negative for tubercle bacilli

but the culture yielded a growth of Staphylococcus albus. The patient improved significantly but a roentgenogram on March 11, 1944 showed more extensive renal calcifications. On May 5, 1944 a recurrent abscess became manifest in the right flank which was drained surgically. Since it was superficial it was not judged to be a perinephric abscess.

The patient was next seen in February 1945, at which time a roentgenogram of the abdomen revealed extensive bilateral renal calcifications. In December 1945, he experienced gross hematuria and at that time passed a calculus. In

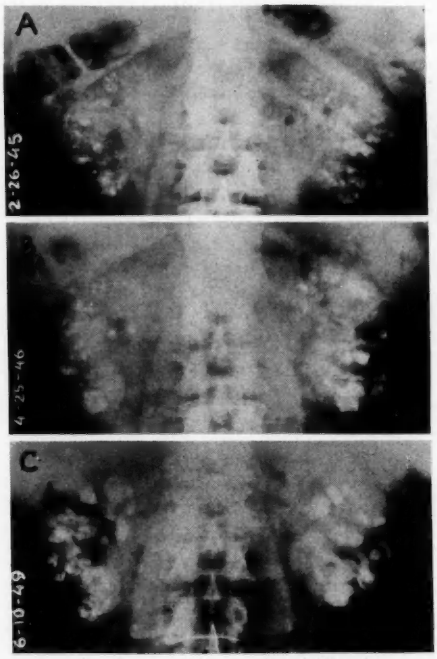

FIG. 3. Showing progressive increase in renal calcifications, case 1. Dates shown on each film.

April 1946, a recheck film of the kidneys revealed a decided increase in the renal calcifications and the patient gave a history of having passed additional stones, many without exceptional discomfort (fig. 3).

He was examined again in June 1949, at which time there was further increase in the amount of renal calcifications and numerous shadows evident in the region of the kidney pelves. An excretory urogram showed limited excretion of diodrast and the kidney pelves were not visualized.

He was next seen in September 1950, when he was admitted as an emergency case because of complete urinary retention due to a stone impacted in the urethra. Efforts to extract this calculus failed and it was finally pushed back into the bladder and removed by litholapaxy. At this time the blood urea ranged

between 74 and 87 mg. per 100 cc. A roentgenogram revealed significant increase in bilateral renal calcification. The left ureter was dilated and was completely filled with multiple small and large stones (fig. 4). The patient's general condition had deteriorated and surgical intervention was considered unwise.

In December he was admitted as an emergency case to another hospital because of ureteral obstruction on the right produced by a calculus. A ureterolithotomy was performed following which the patient became uremic and died. Permission for autopsy was not granted.

FIG. 4. Case 1. A late film showing extensive bilateral nephrocalcinosis with many calculi impacted in lower and midportion of left ureter.

The cause of the initial kidney injury in case 1 is uncertain, although it was probably due to a pyelonephritis secondary to otitis media. The case is particularly instructive, however, in that it clearly shows the progress of even minimal renal calcification to extensive disease associated with bilateral stone formation and ureteral obstruction.

Case 2. A man 26 years of age was first observed in February 1940. He had experienced hematuria 5 days previously, followed by colicky pain in the right flank which was not relieved by hypodermic injection. The pain gradually subsided, however, leaving a residual soreness in the side. He stated that seven years previously he had experienced a similar attack of acute pain in the right flank which had been relieved by a hypodermic. He was uncertain whether or not a stone had been passed at that time.

The general physical examination was without significant positive findings. Urinalysis revealed a specific gravity of 1.015, pH 5.6, a faint trace of albumin but no sugar. Microscopic examination showed 10 to 12 red blood cells and an occasional white blood cell. The blood urea was 42 mg. Plain roentgenogram of the abdomen revealed many small clustered calcifications in the right kidney region and a small cluster in the region of the midportion of the left kidney. An excretory urogram disclosed prompt excretion of the dye and both kidney pelves appeared normal. The calcifications were evident in the renal pyramids distal to the calyces. No ureteral obstruction was demonstrated. It was assumed that the patient had passed a ureteral stone and there were no operative indications at that time.

He was next examined in November 1945, on the recurrence of right renal colic associated with gross hematuria. X-ray examination again revealed the parenchymal calcifications in both kidneys and a shadow in the course of the right ureter. An excretory urogram revealed hydronephrosis of the right kidney pelvis with obstruction in the midureter due to a right ureteral calculus.

Cystoscopy was performed under anesthesia; the right ureter was dilated and the stone manipulated. Several days following this procedure the patient passed a calculus.

He was observed again in December 1946, because of a rather typical left ureteral colic. Roentgenogram showed, in addition to the bilateral renal calcifications, a shadow in the region of the lower left ureter. An excretory urogram revealed a stone well down in the left ureter productive of some ureteral dilatation. Because of its small size management was conservative and the calculus passed spontaneously.

The patient had a recurrence of left ureteral colic in February 1950, and a stone at the lowermost end of the ureter was removed by cystoscopic ureteral meatotomy and extraction. On this examination the urea was 33 mg., the kidney functional test 84 the first hour and 75 the second hour. The chemistry at this time showed a CO_2 of 57 vol. per cent, chlorides 561, calcium 11.0 mg. and phosphorus 3.7. Analysis of the stone disclosed a calcium oxalate calculus.

The urine cultures were repeatedly sterile and at no time were tubercle bacilli found. The patient has not returned for observation.

Case 2 is of particular interest as it represents an instance in which the lesion of nephrocalcinosis is not a diffuse bilateral disease. On the left side the calcification was limited to a single renal papilla and pyramid. Also, the kidney functional studies were virtually normal. There was no abnormality in the chlorides or CO_2 combining power and the patient apparently had sufficient normally functioning renal tissue to maintain these values at average levels.

Case 3. A man aged 45 was first seen at the Clinic in January 1951. Three weeks previously he had experienced acute left ureteral colic lasting several hours and requiring a hypodermic. He believes he later passed a stone, although it was not recovered. X-ray examination revealed numerous clustered calcifications in the left renal area (fig. 5).

The past history disclosed the fact that in the fall of 1949 he had an acute "strep throat" for which a sulfa drug was prescribed. As a result he developed an acute sensitivity with an exfoliative dermatitis and the drug was promptly discontinued. He recalls no urinary symptoms.

Physical examination revealed no significant positive findings. Urinalysis: pH 6.0, specific gravity 1.009 to 1.014, a trace of albumin, sugar negative. Microscopic examination of the sediment showed 10 to 12 red blood cells and 8 to 10 white blood cells. The blood chemistry studies showed a blood urea of 27 mg. and blood sugar 85 mg. per 100 cc. CO_2 combining power 56.7 vol. per cent. Chlorides 627 mg. per cent, calcium 11, phosphorus 3.8 mg. per cent.

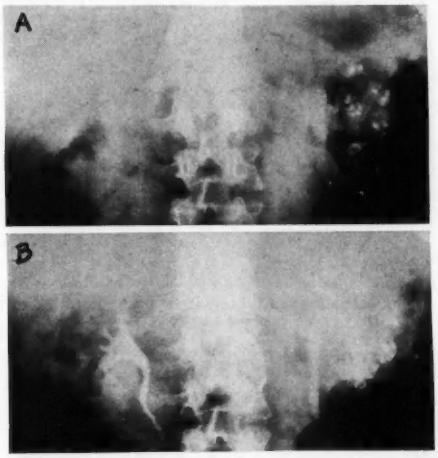

FIG. 5. Case 3. *A*, plain roentgenogram and *B*, excretory urogram showing unilateral nephrocalcinosis.

X-ray examination: plain film showed many calcifications in clusters in the left renal area. An excretory urogram revealed satisfactory excretion of dye. The renal pelves appeared normal. The calcifications on the left side were in the pyramids adjacent to the calyces. Diagnosis: Unilateral nephrocalcinosis, left, with calculi.

Case 4. A woman aged 32 was first seen at the Clinic in January 1948, complaining of kidney stones. She had first developed pain in the left flank in 1943. X-ray at that time was reported as having shown a staghorn calculus in the left kidney. A letter from the attending physician stated that no calcifications were evident in the right kidney. Because of recurrent left renal colic and infection, a left nephrectomy was performed in July 1944. Following this operation the patient received extensive sulfonamide medication but does not recall that this was associated with ill effects.

In the spring of 1946 she had an attack of right ureteral colic and passed a stone. X-ray examination revealed the presence of multiple miliary calcifications in the remaining right kidney (fig. 6). Since that time she has frequently

passed calculi which, on analysis, were found to be composed of calcium phosphate. Blood chemistry and phosphorus levels have been repeatedly within normal levels and hyperparathyroidism has been excluded. Urea clearance

FIG. 6. Case 4. Plain roentgenogram showing typical nephrocalcinosis in a single remaining kidney.

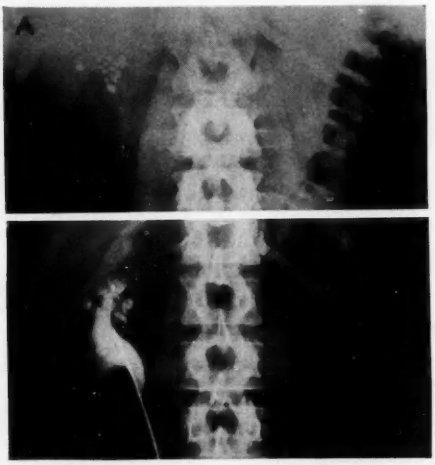

FIG. 7. Case 5. *A*, plain film and *B*, retrograde right pyelogram showing nephrocalcinosis localized to region of upper calyces.

kidney functional test at the time of the first examination was reported as showing 74 per cent the first hour and 73 per cent the second hour. Subsequent blood chemistry studies have indicated the development of mild acidosis.

In September 1950, the CO_2 combining power was 38.1 vol. per cent, in April 1951, 37.2 vol. per cent, and the plasma chlorides 627 mg. per cent.

Since in recent months the patient has been managed by the administration of a citrate mixture and low salt diet, x-ray examination indicates a reduction in the extent of renal calcifications, although not striking as yet.

Case 5. A man aged 45 was first seen in the Medical Department in November 1942, complaining of exceptional fatigue, exhaustion, and spells of weakness. He had also experienced recurrent attacks of renal colic associated with hematuria and the passing of stones which had occurred intermittently for the past 8 years. Previous x-ray examination had been reported as showing "gravel" in the kidney.

The physical examination was without significant positive findings. The blood pressure was normal. A plain roentgenogram of the abdomen disclosed the presence of multiple small irregular calcifications limited to the upper pole of the right kidney (fig. 7). A cystoscopic examination revealed no abnormality in the bladder. The right ureter was catheterized and retrograde pyelogram showed a normal kidney pelvis. The calcifications previously observed were evident in the renal papilla adjacent to the upper calyx.

Urinalysis showed a faint trace of albumin but only a rare pus cell. Examination of the urine was negative for tubercle bacilli.

The patient was again seen in April 1943. X-ray examination showed no significant change in the amount or character of the renal calcification. We have not seen the patient since that time.

DISCUSSION

In none of our cases have we obtained surgical or autopsy specimens of the kidney for histologic study. However, Govan[8] reports the necropsy examination of the case studied by Baines, Barclay and Cooke[9] wherein nephrocalcinosis was observed associated with hyperchloremia and low plasma bicarbonate in a woman 29 years of age. We are interested concerning the findings in the urinary tract:

Both kidneys were enlarged with dilated pelves and calyces which contained many light brown calculi of varying size. Some calyces contained single large stones and others innumerable small stones of similar color. Erosion and ulceration of the pelves were evident, with thinning of the renal parenchyma in addition to multiple stones in the right ureter.

Microscopically the glomeruli were enlarged, many having undergone hyaline obliteration, but there was no evidence of glomerulitis. The cells of the proximal tubules were exceptionally swollen and atypical due to the presence of large vacuoles. The nuclei were pushed to the base of the cells. Degenerative and regenerative changes were evident in the descending portion of the proximal convoluted tubule. Occasional calcification of necrotic cells was observed. Intense fibrosis made identification of the narrow portion of Henle's loop difficult but the ascending limbs were dilated, many containing casts which showed calcification.

[8] Govan, A. D. T.: Quart. J. Med., **19**: 277, 1950.
[9] Baines, G. H., Barclay, J. A. and Cooke, W. T.: Quart. J. Med., **14**: 113, 1945.

More significant changes were present in the collecting tubules. Occurrence of calcification was common both within the tubules and the necrotic epithelium. Calcified masses lay imbedded in surrounding fibrous tissue which appeared to have been extruded from the tubules. The ducts of Bellini also contained calcified material and many showed ulceration and severe inflammatory reaction which extended to the renal pelvis.

The findings in this case represent advanced disease. The patient was known to have had urinary calculi for at least 5 years and had experienced polyuria and thirst since the age of 10, which may have indicated the onset of her disease. However, except that the findings are more extreme, they agree with other reported pathologic studies in nephrocalcinosis[10] and consist of pronounced tubular changes with calcification in the distal and collecting tubules, as well as extratubular calcified concretions in the renal papilla.

We have now observed 12 cases of nephrocalcinosis in which a clinical diagnosis was made by means of roentgen examination of the kidneys. All but two of these patients have formed stones; in many instances the discovery of nephrocalcinosis was made only on consultation sought because of renal colic. As we reflect upon these cases, certain interesting points emerge: 1) I believe we are justified in assuming that the primary trouble is renal tubular damage brought on by some nephrotoxic agent, which may be bacterial or chemical. 2) The calcification follows this tissue damage and occurs chiefly in the distal and collecting tubules and extratubular tissue of the renal papilla. The term dystrophic calcification has been applied to this pathologic process long recognized by pathologists. 3) The tubular dysfunction may give rise to certain metabolic disturbances, notably hyperchloremic acidosis and disturbances in calcium and phosphorus metabolism. Rickets has been observed by Albright. 4) These tubular and papillary calcifications lead to the formation of urinary calculi. 5) As far as the radiologic findings are concerned, this is not always a diffuse bilateral disease; it may be unilateral or localized to only a small portion of the kidney. When one assembles all these facts, the mechanism for stone formation affords clinical support for the ideas propounded by Randall in 1936 and subsequently supported by Keyser.

As a result of clinical observation, extensive autopsy examinations and experimental studies, Randall came to the following conclusions:

1) "That in the absence of stasis, a primary renal calculus is dependent upon and arises because of a pathologic condition of the renal papilla.

2) "The pathologic condition is a varying degree of damage to the structures of the collecting tubules and supporting interstitial tissue.

3) "This damage is succeeded in the living by attempted repair in which calcium salts may be deposited.

4) "Such calcium salt deposition may be both intratubular and extratubular and of varying degree; in some slow, discrete and chronic; in others acute, rapid and overwhelming."

In his autopsy studies two types of lesions in the renal papilla were observed:

[10] Davis, J. S., Klingberg, W. G. and Stowell, R. E.: J. Pediat., **36:** 323, 1950.

Type 1, a calcium plaque predominantly interstitial and showing a slow, chronic course usually situated at the apex of the pyramid; type 2, an intratubular deposition of calcium indicating a more acute and rapidly developing process.

Type 1 is most frequently on the side wall of the papilla and remains harmless until brought to the surface by growth and pressure. Once exposed, it is bathed in urine and, acting as a foreign body, becomes the nidus upon which any urinary salt may crystallize. Thus Randall demonstrated calcium phosphate, calcium oxalate, and uric acid calculi with the same calcium core.

In type 2 the calcium salts were principally intratubular producing tubular damage. Only calcium phosphate was demonstrated in this type and any stone formation occurred at the papillary tip where the morbid process was most advanced. In 1,154 autopsies type 1 was found in 19 per cent, and type 2 in only 1.9 per cent; there were 65 examples of calculus growing adherent to the renal papilla.

Based upon this concept, one may presume that the cases of nephrocalcinosis herein reported represent extreme examples of type 2 lesion.

Randall emphasized the pathologic findings observed in the renal papilla. However the evidence presented by these cases of nephrocalcinosis justifies the concept that the pathologic process may begin even higher, certainly in the distal convoluted tubule and possibly in the proximal tubules.

Even in this group of cases demonstrable by roentgenogram the extent of the injury and resulting calcification are variable. Furthermore, cases of nephrocalcinosis are known to have existed in which the lesion was not demonstrated by x-ray. We may assume that it is possible to have minimal, limited and localized renal tubular damage which is followed by calcification. This small calcific fragment works its way down through the collecting tubules, perhaps as a foreign body, and finally emerges at the tip of the renal papilla. Then, as Randall comments, it becomes the nidus around which urinary salts accumulate to become a calculus, which finally drops off to be passed. This would explain the frequent clinical observation of the patient who passes a single stone and never has a recurrence. Conversely, recurrent stones may be due to more widespread kidney damage or to some constant source of repeated damage to the renal cells. Focal infection deserves consideration.

Perhaps we urologists have become accustomed to thinking of the renal pelvis and the minor calyces as the top of the urinary tract. The problems presented by the disease under discussion indicate that we must consider the collecting tubules and even the nephron in order to understand this and possibly other diseases as well. We have, in these cases, a clear demonstration of what is perhaps the chief mechanism of stone formation. That many of these cases are visible to radiographic demonstration is unfortunate for the patient as it bespeaks extensive renal damage with an uncertain or unfavorable prognosis. However it may serve us, for by analogy we may picture the same process in its minimal form not visible to x-ray until a sizable stone develops. As we learn the causes of renal tubular injury we may also learn the manner in which to prevent many of these primary renal calculi.

DISSOLUTION OF URINARY CALCULI

HOWARD I. SUBY

From the Department of Urology, Massachusetts General Hospital, Boston, Mass.

During the past 13 years much work, relevant and irrelevant, has been done in the laboratory in an attempt to find an efficient yet safe method for dissolving urinary stones. Many interesting and valuable findings have been made, but the solutions thus far concocted have been proved by us to still be impractical in most cases. The fundamentals for treatment of urinary stones have not been changed. Dissolution is definitely the addendum, not the epistle. It is still the side show.

The stone dissolution problem can best be divided into two considerations: 1) theoretical consideration; 2) practical consideration.

THEORETICAL CONSIDERATION

The theoretical problem envisions the stone—chemical substance—in equilibrium with the solution in which it is immersed. This solution may be water, acid, alkali, or salt. In vivo, of course, the stone is in equilibrium with the complex components of the urine. The theoretical principle of stone dissolution is to cause increasing ionization of the stone. Stone ions, adrift in the solution at all times, can be captured by other appropriate ions yielding a soluble product, thus forcing the stone (which must keep up the equilibrium) to give more and more ions and dissolve.

A. Calcium phosphate (*including magnesium ammonium phosphate and calcium carbonate*). In the case of calcium phosphate, the addition of any acid solution provides hydrogen ions and "radical" ions to act as the procurement forces. The hydrogen ions attach themselves to the phosphate ions producing soluble phosphoric acid, and the "radical" ions attach themselves, in various degrees of efficiency, to the calcium ions thus making this part of the stone also soluble. Strong inorganic acids with low pH such as HCl, H_2SO_4, etc. do well but are obviously too iritating to be practical. The value of citrate as an efficient "combiner" with calcium has been known for many years. It is the basis for the use of citrate as a substance to prevent the clotting of blood. A soluble complicated calcium citrate molecule is formed, and this was the rationale for our earlier studies in stone dissolution.

By measuring loss in specific gravity of rabbits' teeth (calcium phosphate) immersed for 8 hours in solutions of different chemical composition, concentration, and pH—an index of efficiency for approximately fifty organic and inorganic acids was established. By testing living rabbits' bladders with all of these solutions it was likewise possible to establish an index of irritation. By pure chance it was noted that certain solutions were rendered much less irritating but no less efficient by the addition of magnesium. This finding led us to propose solution G and solution M as feasible solutions for certain practical

usage. The formula for solution G (pH 4) is:

Citric Acid (monohydrate)	32.25 gm.
Magnesium Oxide (anhydrous)	3.84 gm.
Sodium Carbonate (anhydrous)	4.37 gm.
Water	1,000 cc.

During the time that this experimental work was being conducted—we were also making many experiments with certain water softeners. Calgon (still recommended for automatic dishwashers today) was found to be about equal to solution G in its ability to dissolve calcium phosphate, but it was found to be much more irritating. Moreover, it was impossible to lessen its irritation by adding magnesium.

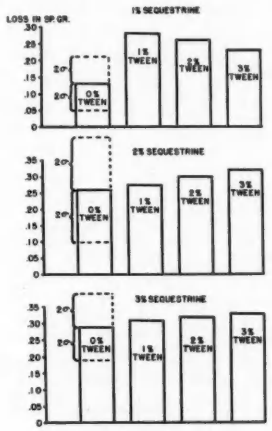

FIG. 1

Our interest in water softeners continued, however, and after World War II in Dr. Fuller Albright's laboratory we did much experimental work with sequestrine (versene acid, ethyl diamine tetra acetic acid). This was supplied to us by the Alrose Chemical Company of Providence, Rhode Island and their Mr. Zussman gave us much advice regarding its use. This was the same substance (calsol) that was reported by Dr. Gehres and by Dr. Abeshouse at the 1950 meeting of the American Urological Association. The results of our experiments with this acid were encouraging but in strengths of good efficiency, sequestrine was found somewhat more irritating than solution G. We have continued and are continuing our work with this solution.

In an attempt to speed dissolution, wetting agents have been added to the solvents. Wetting agents, used in detergents, theoretically bring the solvent closer to the solute. Tween 80, a wetting agent made by the Atlas Chemical Company, enhanced the solubility effect of sequestrine in our first experiments. This was especially marked with the 1 per cent sequestrine solution and sent our hopes high (fig. 1). Later and more carefully controlled experiments, how-

ever, failed to confirm these results. Other wetting agents are being considered for it certainly seems that this phase of the work may be of great importance.

B. Calcium oxalate. Calcium oxalate stones are about the most prevalent primary urinary stone, and they are also often the hardest and the most difficult to attack by dissolution. Solution G has very little effect on them. It is a fact that versene acid does have more effect on calcium oxalate stones than does solution G. This is shown in figure 2. It is noted that the weight of calcium oxalate stones immersed in 2 per cent sequestrine definitely decreases. The graph looks encouraging but this amount of dissolution is impractical. Unless a stone of this comparable weight is completely dissolved in 50 to 75 hours, we have learned that the solvent used is relatively impractical. We have speculated regarding the use of bacteria or ferments on oxalate stones. Agricultural chemists

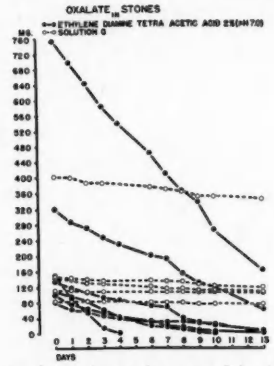

FIG. 2. Weight of calcium oxalate stones immersed in 2 per cent sequestrine solution and in solution G.

tell us that certain soil bacteria grown on media containing oxalic acid will and do ultimately dissolve oxalate, but Father Time may be too slow for a patient with a renal stone. Some encouraging experiments using ferric chloride solution as the solvent have been conducted. This is still in the impractical stage, however.

URIC ACID

Uric acid stones and crystals have been subjected to many types of alkaline solutions (sodium hydroxide, sodium bicarbonate, sodium borate, lithium borate, etc.) but results so far have suggested that the dissolution effect of each of these solutions has been dependent upon the pH. The higher the pH of the solution the more efficient the solubility effect on uric acid. Gehres reported that versene acid had good solubility effect on all stones. We have been unable to substantiate that. Figure 3 shows the decrease in weight of uric acid stones immersed in 2 per cent versene acid (pH 7.0) for 14 days. The same figure shows that uric acid stones immersed in a buffered watery solution at pH 7.0 dissolved just as rapidly (precisely the same rate) as did those in versene acid. The pH of the solution again seems to be the important factor.

Whereas it is usually improbable that alkalinization of the urine will cause dissolution of uric acid stones in patients, it is becoming better established that this form of therapy is of unquestionable importance in preventing further formation of uric acid stones. We usually advise a low purine diet plus sodium citrate—two grams four to six times a day, and have the patient test his urine with nitrazine paper to keep the pH at 7.5.

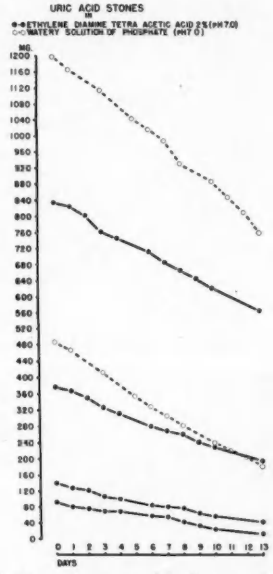

FIG. 3. Weight of uric acid stones immersed in 2 per cent sequestrine (pH 7.0) and in a buffered watery solution at pH 7.0.

CYSTINE STONES

What has been stated regarding the dissolution of uric acid stones applies in essence to the problem of dissolution of cystine stones. So far we have found no good solvent for cystine that has not been extremely alkaline. A solution at pH 10 is much more effective than one at pH 9. This is shown in figure 4. We do feel that alkalinization of the urine is advisable in these patients to help prevent recurrence.

PROTEIN MATRIX

Attack on the protein matrix, although important, is probably of less importance than attack on the inorganic stone substance. If the inorganic salts are dissolved—the castle usually crumbles and piece by piece is washed away. By dissolving "sludge," however, it is possible that inorganic salts are for the first time exposed to the inorganic solvent. Experiments with many proteolytic enzymes have been done, but these have not produced convincing results. Inactivation of enzymes at certain pH levels has made their use impractical

with many solutions. We have recently done experiments using desoxyribonucleoproteinase (dornase) on urinary sediment. Dornase has been proved a good proteolytic enzyme for dissolving pleural effusions etc. by Tillets et al. of New York City. We have used the Feulgen stain to test the solubility effect (fig. 5). Our practical problem of course is different from that of a closed pleural space where dornase can be locked and kept dormant for many hours at a time.

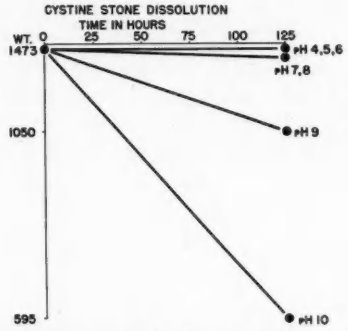

FIG. 4. Weight of cystine stones in buffered solutions of different pH levels

FIG. 5. Feulgen stained specimens treated with dornase

We are working in a moving stream, and this enzyme may be washed away before it can do its magic.

PRACTICAL CONSIDERATION

Time and space preclude the possibility of our discussing the entire problem of mechanically getting and keeping the solution in contact with the stone. As we have stated previously, this will usually be dependent upon the patience and ingenuity of the attending urologist. Simplicity is of greatest importance, however, if the patient is to do his own irrigating, and the shortage of nurses and attendants have usually necessitated this plan.

There are two simple basic methods of irrigation which can be utilized. The first entails running a constant flow of solution through an inlet tube and allowing its constant escape from the kidney or bladder through an outlet tube. There are two main objections to this method. The first is that it requires a

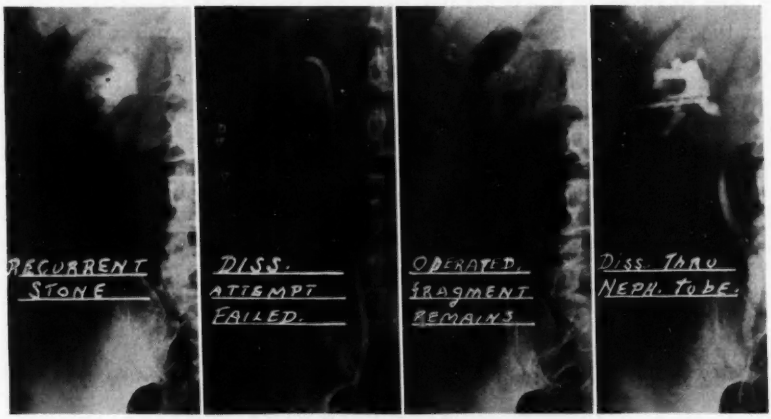

FIG. 6. Case 1

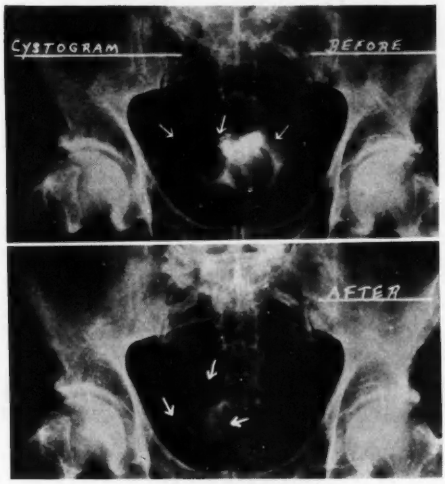

FIG. 7. Case 2

large amount of solution which actually does not do its full capacity of work. This is expensive and bulky. The second objection is that there is a good possibility that the stone is only partially touched, or even completely missed, by the migrating solution which is constantly seeking the route of least pressure and eventually the outlet tube. In other words, there is danger of the "magenstrasse" effect. By raising the outlet tube some of this bad effect can be eliminated.

The second method of irrigation is the intermittent closed type which allows a certain amount of solution to enter the kidney or bladder, locks it there for a certain length of time, then allows it to drain for a specified period of time. Although this method has the disadvantage that the solvent is diluted by the urine excreted during the "locked in" period, it has the advantage that it insures that the stone is surrounded by the solution. It also has the advantage that it

FIG. 8. Case 3

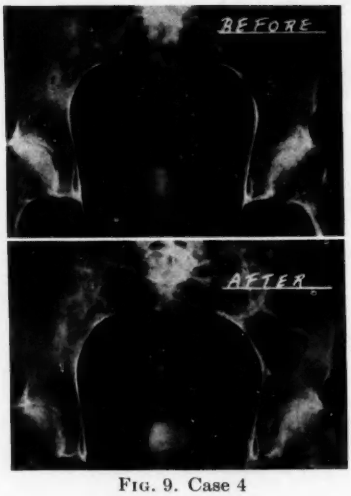

FIG. 9. Case 4

allows spells of complete rest for the kidney or bladder—a fact of great importance in preventing fever, pain, or bleeding. We have preferred this second method.

Seven cases who have had trials of irrigation with 2 per cent versene acid are presented. This is obviously a preliminary report, but it is timely.

Case 1 (fig. 6): A 37 year old man with recurrent right renal stones attempted dissolution with solution G through a ureteral catheter; this was unsuccessful. Right nephrolithotomy was done but two small fragments were left. Sequestrine

(2 per cent) irrigations through a nephrostomy tube were tried but caused the patient such severe pain that they had to be omitted. Solution G irrigations caused patient no pain.

Case 2 (fig. 7): A 72 year old man with 3 nonopaque bladder stones was irrigated intermittently with 2 per cent sequestrine. He had very severe pain,

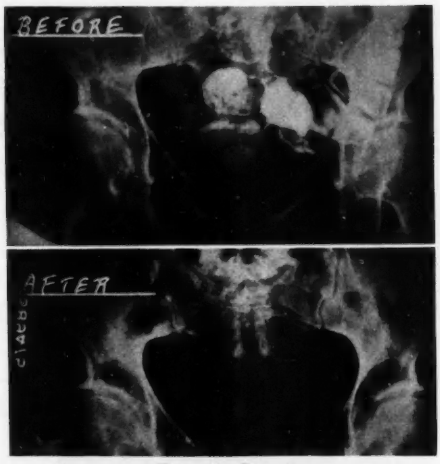

FIG. 10. Case 5

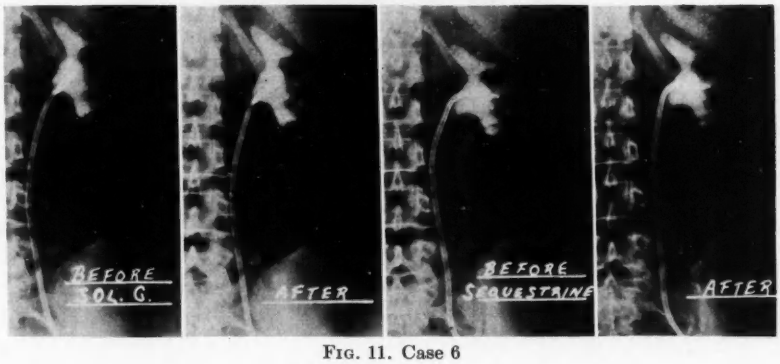

FIG. 11. Case 6

and after a few days the stones were removed by suprapubic cystostomy. There had been no evidence of dissolution.

Case 3 (fig. 8): A 70-year-old man with a single bladder stone attempted dissolution by intermittent irrigation with 2 per cent sequestrine. He had so much pain that only a few hours of irrigation could be tried. Dissolution with sequestrine was obviously impractical, and his stone was removed surgically.

Case 4 (fig. 9): A 30-year-old paraplegic with a single large bladder calculus used intermittent irrigations of 2 per cent sequestrine, but fever and bleeding

occurred. Sequestrine 1½ per cent was tolerated better, and the stone became smaller. She is continuing irrigations at home.

Case 5 (fig. 10): A 71 year old man with two bladder stones attempted dissolution with 2 per cent sequestrine but the pain was intolerable. The stone was removed surgically.

Case 6 (fig. 11): A 39 year old woman with bilateral renal stones showed no evidence of dissolution with solution G through a ureteral catheter. She was then irrigated with 2 per cent sequestrine solution, but the pain was intolerable. Irrigations with 1½ per cent sequestrine were then done 6 or 7 hours daily for 10 days, but there was no evidence of dissolution.

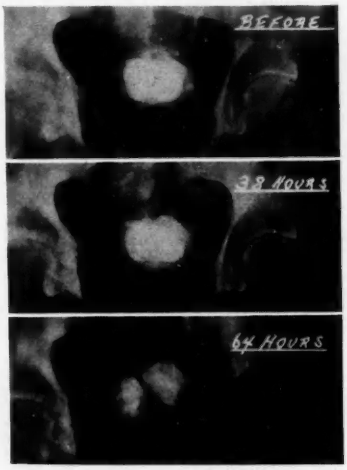

FIG. 12. Case 7

Case 7 (fig. 12): A 54 year old paraplegic with four large bladder calculi was irrigated intermittently with 2 per cent sequestrine solution. He tolerated the solution poorly, voiding it around his catheter, and in spite of his paralysis, experienced pain in the bladder and legs. The stones were removed surgically.

Whether or not this small group of cases had unusually sensitive bladders and kidneys is questionable, but the trials did seem to indicate that 2 per cent sequestrine was quite irritating and very painful. Our laboratory technicians have noticed this fact also—complaining of severe pain if they accidentally got a little sequestrine onto a crack or cut in their hands.

No one knows more of the trials and tribulations of stone dissolution than do those who have spent time working on the problem. By subjecting our failures to careful scrutinization we are attempting to better our judgment and techniques. The problem is extremely interesting and should gain in practical importance as more careful work is done, but it is a long and difficult problem. It is still the sideshow.

262 Beacon St., Boston 16, Mass.

DISCUSSION

Dr. George Gilbert Smith (Brookline, Mass.): I should like to say a few words about nephrocalcinosis in connection with Dr. Engel's presentation. I have two patients who have that condition. Here are some slides which I should like to show you. They are rather interesting because, in contradistinction to some of his cases, they show the period of time that may elapse with very little change.

(Slide) This was a woman who was 28 in 1938 when I first saw her. In 1931 she started passing small renal calculi. She was very much troubled by them. She was studied by Dr. Albright who did not think she had hyperparathyroidism.

This slide was taken in 1938. The stones in this slide do not show up very well, but if you look very carefully, you will be able to see them.

(Slide) This is a slide taken in 1949. In that time this woman had had three children. Her NPN in 1938 was 27 mg. per cent. A recent one was 31 mg. per cent.

Her PSP in 1941 was 70 per cent in two hours. With the first pregnancy, she had several attacks of rather sharp bleeding from the left kidney. As the ureters and pelves were dilated, the stones began to rattle out very rapidly, but she never had a stone that stuck in the ureter very long.

Her last two pregnancies were practically uneventful. Except for an occasional attack of hematuria of a very slight degree, she has been comfortable. She still has a urinary infection at the present time. Her specific gravity is quite fixed, varying from 1006 to 1010 but her blood pressure is not elevated.

(Slide) This patient was also 28 when she was first seen in March of 1945. There are a great many small shadows in the lower poles of both kidneys. When I first saw her, she had a ureteral calculus obstructing one kidney, and that calculus had to be removed. She has had two children. She is in good general condition now; her blood pressure is not elevated (120/82). Her NPN is 28 mg. per cent. The specific gravity has been between 1010 and 1019. She occasionally has hematuria, but very little in the way of symptoms, and she feels very well.

I do not know how long these cases will go before the kidney functions deteriorate to a point where the patient's health is affected but the small calculi in these two cases have not tended to form large stones.

Dr. Edgar Burns (New Orleans, La.): I believe that a word of caution should be sounded regarding the use of the new antibiotics in the treatment of urinary infections. During the past two months, I have run across three cases which I think should be called to your attention.

Two deaths occurred from aplastic anemia following the administration of chloromycetin. One of the cases might be questioned for the reason that other drugs were used in a somewhat limited amount; however, chloromycetin was the major drug given and for a long period of time. There could hardly be any question about the second case since chloromycetin was the only drug used.

The third case appeared in the literature within the past three weeks. A death occurred from aplastic anemia following administration of streptomycin. I believe we have been inclined to feel that a great many of these newer drugs are entirely safe, but they apparently have side reactions which are just beginning to crop up now, and some of these are important.

DR. JOHN K. ORMOND (Birmingham, Mich.): In your paper, Dr. Engel, you spoke of sulfonamides. Was there, in every case, clinical toxicity from the use of sulfonamides, or were there cases in which sulfonamides were given over a long period of time without any clinical evidence of toxicity?

DR. DAVID M. DAVIS (Philadelphia, Pa.): It seems to me that, from the point of view of the surgeon, the one item in the causative elements of urinary calculi which should receive a great deal of attention is that of obstructive stasis. This is so, not necessarily for the reason that it is the most important element in the causation of the stone, but because it is something which we can correct; at least we can try to correct it. That is not true of some of the other causative elements in the stone situation.

If one accepts this idea, the surgeon should assume that there is some obstructive stasis present in every stone case, and look for it. If the search is unsuccessful, he should not conclude that it is not there, he should only conclude that perhaps it is there, but he has not been able to find it. If by relieving obstruction one ever prevents recurrence, one has done the patient a great favor. The slides I have illustrate a case in point.

(Slide) This woman had pain in the left side with fever. The right kidney pelvis appears normal. On the left side is a half pelvis with a ureter which is approximately normal in diameter. Outside the ureter shown are two large stone shadows, the upper one much larger than the lower. The cystoscope showed a ureterocele surrounding the lower stone. The opening of the ureterocele was so small I was unable to catheterize it. There was another orifice alongside the ureterocele giving entrance to the other ureter. In short, there was complete pelvic and ureteral duplication on the left with hydronephrosis of the upper pelvis, hydro-ureter of its attached ureter and two large ureteral calculi, all consequent upon ureterovesical obstruction. The excretory urogram showed nothing in the upper part of the left kidney. The top of the ureterocele was cut off and its contained stone was removed. The dilated ureter was exposed outside the bladder. Its wall was found to be almost a quarter of an inch thick, an enormous muscular hypertrophy, due to lifelong obstruction. It was full of thick purulent material which bore no resemblance to urine. The stone was removed, and nothing further was done.

(Slide) The next picture was taken eight or ten months later. The two ureters are easily visible on the left side. The pelvis which lay at the top of that enormously dilated hypertrophied ureter and the ureter itself have returned practically to normal. The urine is clear and sterile, and the patient is free of symptoms. All that took place about 5 years ago, and the situation still remains the same. I do not anticipate that the patient will have any more stones.

Dr. George R. Livermore (Memphis, Tenn.): About twenty-five years ago, I wrote a paper on nephrolithiasis, and I made the statement that I thought infection, stasis, and metabolic changes were responsible for stones in the kidneys.

Some years later, we investigated the production of stones in rats by using a vitamin A and D free diet, and we were able to produce a number of stones in a great number of rats. The problem is: Do rats and people react the same?

Dr. Wyland F. Leadbetter (Boston, Mass.): Dr. Engel made the observation that in cases of nephrocalcinosis, he had not seen an operative or autopsy specimen. I have had a case which illustrates this. This was a woman of thirty who passed stones repeatedly from the left side. You will see her x-rays.

(Slide) There is a group of stones in the lower calyx and a group in the upper calyx which might appear to be in the pelvis; actually, they are not. You can see, here, that the stones actually lie in the upper and lower pyramids. The x-rays do not show stones in any other part of that kidney, or in the opposite kidney. The urine was sterile.

(Slide) We explored this kidney and took off the upper pole of the kidney and made an incision in the lower pole and removed the calculi in the lower pyramid.

This is the postoperative film. The kidney is functioning. Over a period of months, there has been no recurrence in the upper part, but there is recurrence of stones in the lower pyramid.

(Slide) This is the upper part of the kidney which is removed. You can see the stones scattered through the pyramids.

(Slide) We sectioned the kidney tissue and this shows a section of the upper pyramid which contained the stones. The spaces were occupied by the calculi. Each space is lined by tubular epithelium.

This brings up a small point which relates to a possible congenital anomaly of the collecting tubules of the kidneys. The French have described what they call a "sponge kidney" in which there are congenital dilatations in the terminal collecting tubules. I have seen, in the last few years, several cases falling into that category.

Possibly the development of stones intrarenally or in pyramids might be on the basis of congenital abnormality in the tips of pyramids.

Dr. George R. Livermore (Memphis, Tenn.): I should like to ask Dr. Priestley a question. Some years ago we did some experiments on transplanting muscle and fat in the kidneys. There was some damage following the transplantations. Dr. Priestley did not say anything about his use of oxycel gauze or anything for controlling hemorrhage. Does oxycel gauze damage the kidneys or not?

Dr. Ira Sisk (Madison, Wis.): What I have to say is perhaps of little importance but it relates to the use of basic aluminum carbonate gel in the prevention of calcium phosphate stones as mentioned by Dr. Higgins. Observation over a long period of time is necessary to prove anything about the value of such substances, but I recently had an unusual opportunity to test the substance, and perhaps you will be interested in hearing about it.

About eighteen months ago I removed from the right kidney of a man four stones composed almost entirely of calcium phosphate. About a week after he left the hospital, he again began to have pain and he began to pass daily a large number of small round stones composed of calcium phosphate. When he came to the office every two or three days he would bring a little bottle containing a large number of these stones. As all stones had been removed from his kidney it was obvious that these were being formed from day to day. The bladder was examined, and found to be free of stones but the urine was infected with a colon bacillus. As this seemed to be an ideal time to test the value of basaljel, all other treatment was discontinued and basaljel was given for several weeks. I could see no effect upon the formation of the stones.

Following this a regimen of acidification with drugs and diets was instituted, and within a few days all stone formation ceased. Under this regimen a full year has now passed without the formation of stones.

Dr. Austin I. Dodson (Richmond, Va.): I live on the edge of a stone belt, if such things exist in this country. The large series of stones reported in this area seem to be somewhat out of proportion to the number of stones reported in many other sections of the country.

I have noticed in my practice, which comes partly from the eastern section of Virginia, the Piedmont section of Virginia, and North Carolina, that I have a larger proportion of patients with stones from this area than from the western part of Virginia and from Tennessee and West Virginia, where I also have occasion to see patients.

I know that for a period of more than 100 years, this area that I think of as the stone belt has been the area in which mostly tobacco, peanuts and cotton are grown. I know that particularly as far as tobacco is concerned, the farmers do not use any type of organic fertilizer. They depend on chemical fertilizers for the growth of this crop because anything else would ruin the texture of the weed. I wonder whether the constant impoverishment of the land over this long period of time may have had anything to do with the crops grown for food. Possibly these people are suffering from a long period of diet deficiency.

I do know that in this area are many sharecroppers who are so intent on raising a tobacco crop for money, that they do not even have a vegetable garden. They exist on corn, bleached flour, molasses and hog meat.

In recent years there has been more crop diversification and more cows raised. It will be interesting to see if, in after years, there will be a decrease of stones in this location. Possibly this observation may have some importance. It certainly will if a diet deficiency has anything to do with stone formation.

Dr. William J. Engel (Closing): Dr. Ormond asked a question regarding sulfonamide intoxication. In the original group of seven cases which I reported there was a definite history of sulfonamide medication in six. In the first child the evidence was rather clear cut that the original kidney damage was due to the direct toxic action of a sulfonamide. The patient's brother also gave a history of sulfa medication for sore throat when he was a much younger child. Red urine had been observed by the mother but no other symptoms of toxicity were noted.

It is thought possible that sulfonamides may produce renal tubular damage without giving rise to clinical manifestations of sufficient severity to attract attention. Dr. Jean Oliver who made remarkable nephron dissection studies showed that there was disruption of the distal convoluted tubules in sulfonamide intoxication. This could be followed by calcification.

I do not believe that sulfa intoxication accounts for all cases but I am led to suspect it is a common cause for the tubular damage which precedes calcification.

We have one case in which the degree of calcification has not advanced over the year. However the ones presented here associated with urinary calculi seem to indicate an advancing disease.

Dr. Leadbetter's case may represent another type of condition. I do not believe that all cases of nephrocalcinosis occur in the same manner. It may be that there is a type of congenital dilatation of the collecting tubules in which calcification occurs. Attention has been called to the fact that calcifications may gather in the ducts of Bellini which are the dilated terminal portion of the collecting tubules.

Dr. James T. Priestley (Closing): In reply to Dr. Livermore's question, I wish to say that I have not used gelfoam, but I have used fat or muscle over the end of a kidney in which a partial resection had been done and difficulty was experienced with bleeding. There were no deleterious effects so far as I know. I have no other remarks to make at this time.

CONGENITAL MULTILOCULAR BLADDER: A CASE REPORT

FEDOR L. SENGER AND VINCENT J. SANTARE

From the Department of Urology, The Long Island College Hospital, Brooklyn, N. Y.

Congenital bladder divisions occur so frequently in clinical urology that many men have considered such anomalies of only academic interest. The multiplicity of classifications and the variations in terminology of congenital bladder divisions have resulted from this limited attention. Through the presentation of a case report of a congenital multilocular bladder, it is the purpose of this paper to define the terminology and proffer a simplified classification.

Bladder division has been selected as the general term because its extension includes reduplication of the bladder, septal divisions, contraction rings and cystic loculations of the bladder. Diverticula. which are by definition outpocketings rather than partitions, are excluded. The proposed classification is outlined as follows:

Congenital Bladder Divisions

1) Sagittal or Longitudinal Divisions
   A) Complete reduplication of the bladder (fig. 1, *A*)
   B) Incomplete reduplication of the bladder (fig. 1, *B*) (vesico-bipartite)
   C) Complete sagittal septum (fig. 1, *C*) (vesico-duplex)
   D) Incomplete sagittal septum
2) Frontal or Transverse Divisions (fig. 2)
   A) Complete frontal septum
   B) Incomplete frontal septum
   C) Hour-glass bladder
3) Multilocular Bladders (fig. 3)

Diverticula can be differentiated from bladder divisions by the usual criteria. A diverticulum usually does not have a muscular coat, or the muscle has been thinned out; although the septum in a division may not have a muscular coat, some part of the wall of the division is continuous and identical with that of the bladder. A diverticulum invariably has an opening into the bladder which is usually small. In divisions the communications may be of any size or entirely absent. A diverticulum rarely has a ureter opening into it whereas in divisions, each loculus usually has at least one ureter except in the hour-glass type. Finally, diverticula are most frequently secondary to obstruction; and other changes are found, such as trabeculation, cellules and hypertrophied musculature.

Sagittal or longitudinal divisions of the bladder form two bladders or partitions of one bladder by a cleavage plane or septum which divides the organ into right and left sections. Many embryologic explanations have been offered for this phenomenon, but the evidence seems to indicate that they represent various stages of splitting of the bladder anlage; complete separation results in two bladders or reduplication. Sagittal septa and incomplete sagittal septa are

produced depending on the extent of separation. In all ten cases of complete reduplication cited by Burns, there was reduplication of other cloacal organs.

A reduplicated bladder is defined as two distinct and separate bladders, each having a urethral orifice. In incomplete reduplication, there are two compartments separated by an indentation in the external contour of the bladder and not merely a septal separation.

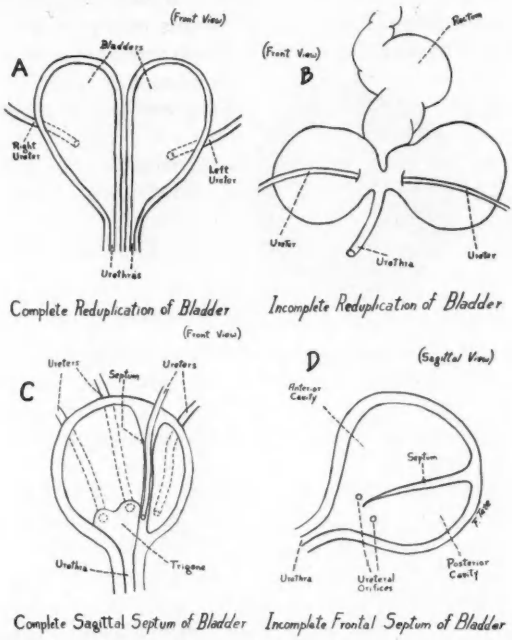

FIG. 1. *A*, complete reduplication of bladder showing two bladders, each with own urethral orifice. *B*, in incomplete reduplication of bladder, one urethra drains both compartments whose separation is evident in external configuration of bladder. *C*, sagittal septum divides bladder into right and left portions without indentations in external configuration. Incomplete sagittal septum does not extend full longitudinal diameter of bladder. *D*, frontal septum divides bladder into anterior and posterior compartments. In hour-glass bladders, septum is short and contraction ring extends around entire transverse circumference.

A complete sagittal septum walls the bladder into two chambers without change in the external configuration. An incomplete septum is one in which the septum has an opening.

Frontal or transverse divisions of the bladder occur less frequently. There are two favored embryologic explanations: The first is that there is an excessive constriction between the urogenital and vesico-urethral portions of the ventral cloaca, which results in a frontal septum, or sometimes, into an hour-glass contraction. The second explanation postulates a supernumerary cloacal septum which indents the epithelial wall of the bladder and carries with it an evagina-

tion of peritoneum. Hour-glass bladders are included in this group. In Caulk's 2 cases and Young's 5 cases of congenital hour-glass bladder, the transverse bands or septums were found only in the posterior portions of their bladders. The hour-glass appearance seems to be due to spastic contracture of the musculature in the same circumference as the anatomical transverse septum.

We have found only 1 case in the literature of complete frontal septums, that of Schwartz, in a female. The anterior bladder was drained by the normal urethra, the posterior by a meatus below the first. The patient had incontinence from the posterior bladder which had a capacity of 80 cc. Young wonders if this was not

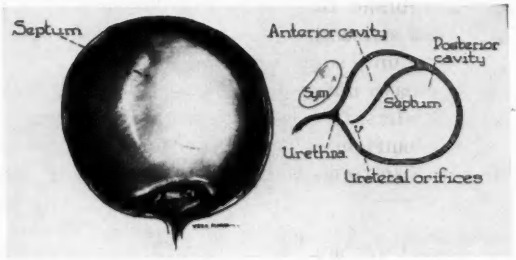

FIG. 2. Sagittal view of frontal septum and appearance of septum through cystotomy incision.

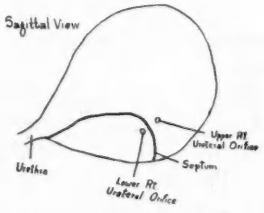

FIG. 3. Multilocular bladders have bladder within bladder. Loculus extends out from trigone and may not communicate with bladder cavity.

a case of cystic dilatation of the lower end of a supernumerary ureter with an opening into the vestibule.

Congenital multilocular bladders of ureteral origin make up the last division. Their occurrence is more frequent and necessarily of clinical interest because there is an associated ureteral obstruction. The loculus always contains a ureter, its posterior portion is normal bladder wall. The intravesical septal portion is lined on both sides with mucous membrane but the intervening tissue is fibrous. In considering their formation Edward's description follows:

"On other occasions it appears that the ureter has failed to perforate the mucosa and submucosa of the bladder wall although the remainder of the tube is patent and it passes through the muscularis. The absence of muscle fibers in the interlocular septum is in favor of this interpretation, as the bladder musculature appears at a later stage of development than the union of bladder and

ureter. In such a case the second loculus is really a cystic dilatation of the lower end of the ureter occurring in the bladder cavity. The cyst may subsequently perforate in which case there is a communication between the two cavities but failing such a perforation the cyst remains isolated from the body surface."

Chwalla's findings support the above descriptive explanation. In embryos between 20 to 28 mm. he found that the ureters are closed off from the bladder proper by membranes. If these persist the secretions of urine balloons the membranes to form secondary chambers, within the bladder but with no communication to the lumen of the bladder. Thus, a loculus is formed due to failure of perforation of this membrane. Brown reports that in mice whose metanephros secretes on the fifteenth or sixteenth day, a hydro-ureter and hydronephrosis are found for 4 to 5 days later until some lower ureteral obstruction is relieved.

Multilocular bladders have not been subdivided but there can be as many loculations as there are ureters. In so far as these locules appear to be of ureteral origin they usually are found in the base of the bladder. The ureter almost always shows evidence of back pressure.

CASE REPORT

A 16 year old white girl was admitted to the Long Island College Hospital on June 27, 1950 with complaints of intermittent, colicky, abdominal pains in both lower quadrants for years. Associated with the pains were bouts of fever, pyuria and dysuria.

Physical examination showed a pale, thin, undernourished girl with pain but no tenderness in the lower abdomen.

Laboratory reports: Red blood cells 3.90, hemoglobin 11 gm., white blood cells 7,350, urea nitrogen 17.8 mg. per cent, creatinine 1.8 mg. per cent, chlorides 599 mg. per cent, CO_2 content 61.6 volumes per cent. Urea clearance 6.1 per cent average normal function. Phenolsulfonphthalein excretion 5 per cent in 2 hours. Urine showed a specific gravity of 1.005; 3 plus albumin and many red blood cells and white blood cells.

Cystoscopy on June 28, 1950 showed a large dilated bladder. Dilated right and left ureteral orifices were seen. Extending from the interureteric ridge around the sides of the bladder to the internal urethral orifice was a septum in which a small perforation was seen. Retrograde pyelograms demonstrated bilateral hydro-ureters and hydronephroses. Cystograms gave the added information that there was complete reduplication of the right kidney and ureter demonstrated by reflux of sodium iodine up the ureters (fig. 4).

From the foregoing findings it was deduced that this was a bilocular bladder and complete reduplication of the right kidney. The ureter from the lower pole of the right kidney and the left ureter emptied into the bladder above the septum. The orifice of the ureter from the upper right kidney was below the septum.

On July 5, 1950 a cystostomy was done. The septum was found as described. It was circular, biconcave with a $\frac{3}{4}$ inch margin attached around the base of the bladder. There was a small perforation in the septum. The septum was completely excised forming one bladder cavity (fig. 5). Below the septum the

other right ureteral orifice was found to be greatly dilated. The bladder neck was found to be adequate. A Pezzer tube was inserted.

The patient's course was uneventful. She was sent home on the thirteenth postoperative day with the Pezzer tube in situ. After 2 months of suprapubic

FIG. 4. Oblique cystogram of patient demonstrating bilateral ureteral reflux of iodide, eduplicated right kidney and marked hydro-ureter and hydronephrosis. Bladder and roculus have been marked in.

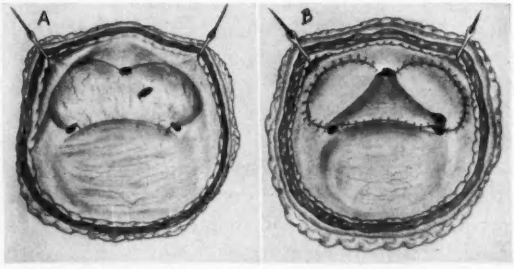

FIG. 5. *A*, view into bladder at time of operation shows septum extending from interureteric ridge around lateral walls of bladder to point below urethra. Two dilated ureteral orifices are seen. Ragged perforation in septum probably was made at time of cystoscopy. *B*, septum has been excised and lumen of bladder is continuous. Second right ureteral orifice which had been below septum is now visible. Attachment of septum was so broad that sutures were necessary to secure hemostasis.

drainage the tube was removed and the cystostomy wound was healed. The patient has gained 20 pounds in weight, is active in school and is much better. Repeat cystograms show persistent ureteral reflux but the hydro-ureters have diminished considerably. Her urine shows a few pus cells. On January 12, 1951 the urea nitrogen was 15.4 and urea clearance was 20.7 per cent average normal

function. The pathologist reported that the septum consisted of connective tissue lined on both sides by squamous and transitional epithelium. No smooth muscle was found in the septum.

DISCUSSION

Wehrbein, Michelson, Edwards, Mezan and Boulgakow and Malek have reported cases of multilocular bladder. There are undoubtedly many others which have been classified as sagittal or frontal septal bladders or even as ureteroceles. Our inclination is to regard ureteroceles as having the same embryologic formation as loculated bladders. In both conditions the ureteral membrane rails to rupture completely. If there is a small perforation the membrane balloons out into a ureterocele. If there is no opening, a loculation is formed in the bladder which may, however, rupture at a later date when the septum has fully formed.

Congenital bladder divisions have been classified into three main categories: sagittal, frontal, and loculated bladders.

Although the last group could be fitted into the first two divisions on the basis of the gross anatomical appearance of the septum, it is our conviction that multilocular bladders deserve a special consideration. Embryologically their formation is different and moreover, they have special clinical significance. In all multilocular bladders there is obstruction to one ureter. The secretion of urine into this closed loculus can form a bladder within the bladder which often interferes with the other ureter or ureters. A report has been given of a multilocular bladder with advanced urologic damage which achieved a good result upon recognition and excision of the septum.

144 Joralemon St., Brooklyn 2, N. Y.

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UROLOGIC ABNORMALITIES ASSOCIATED WITH CONGENITAL ABSENCE OR DEFICIENCY OF ABDOMINAL MUSCULATURE

LAURENCE F. GREENE (by invitation), JOHN L. EMMETT, ORMOND S. CULP

Section on Urology

AND (by invitation)

ROGER L. J. KENNEDY

Section on Pediatrics, Mayo Clinic, Rochester, Minn.

The prime purpose of this report is to describe the abnormalities of the urinary tract which we found associated with the syndrome of congenital absence or deficiency of abdominal musculature and the methods of treatment which we employed. Fifty-seven cases have been described in recent splendid reviews of this condition (Eagle and Barrett, Housden, and Silverman and Huang). We wish to report 5 cases, 1 of which (case 1) was reported in part previously (Daut and associates).

The syndrome occurs predominantly in males; of the total 61 cases reported, including our own, the patient was female in only 3 instances. The basic feature of the syndrome is partial or complete absence or deficiency of the transverse, rectus, internal and external oblique abdominal muscles. The most common abnormality of the urinary tract is hypertrophy and dilatation of the bladder which may assume tremendous proportions. Extreme dilatation and tortuosity of the ureters with obstruction at the ureteropelvic or ureterovesical juncture have been reported. Hydronephrosis, cystic degeneration and atrophy of the kidney have been observed. Patent urachus, obstructions at the vesical neck and atresia of the urethra have been noted. Other common anomalies are bilateral cryptorchidism, "pigeon breast" deformity, malrotation of the gastrointestinal tract and some form of talipes.

Two theories of the cause of this syndrome are commonly proposed. The first theory, and the one to which we ascribe, was postulated by Stumme in 1903. He suggested that obstruction at or distal to the vesical neck exists in utero and results in distention of the bladder with secondary ureteral dilatation and hydronephrosis. As a result of pressure by the distended bladder against the abdominal wall, atrophy of the muscles occurs. The second theory suggests that faulty development of the abdominal musculature is the primary defect, and that the urinary abnormalities are secondary. Proponents of this theory believe that absence of the abdominal muscles, which constitute accessory muscles of urination, permits incomplete emptying of the bladder with resultant dilatation of the bladder, ureters and kidneys.

Thus, according to each of the commonly accepted theories, the destructive changes in the upper part of the urinary tract are secondary to vesical distention, and it is our opinion that surgical efforts directed toward relief of this distention should be made. Therefore, proceeding on a principle previously tried and proved that vesical distention has its basis in an imbalance of the detrusor urinae muscle and the vesical neck (Emmett), we performed resection of the

vesical neck in 4 of our 5 cases with gratifying results; complete atresia of the urethra precluded this operation in the fifth case.

REPORT OF CASES

Case 1.—A boy, 3½ years old, was brought to the Mayo Clinic in May 1945, because "an absence of his stomach muscles" had been noted since birth. The child had experienced recurrent episodes of fever and constant dribbling of

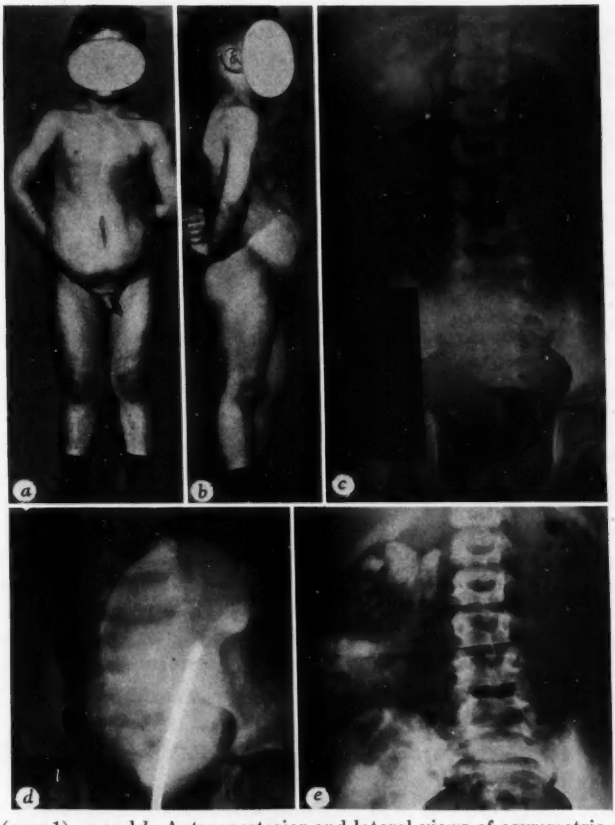

FIG. 1 (case 1). *a* and *b*, Anteroposterior and lateral views of asymmetric deformity of abdomen with midline crease. *c*, Excretory urogram in May 1945. Moderate right hydronephrosis and nonfunctioning left kidney are noted. Tremendous right ureterectasis poorly shown. *d*, Retrograde cystogram. Large, irregular vesical outline is shown. *e*, Excretory urogram made in March 1951. Right hydro-ureter is visualized better but there is no essential change as compared with figure 1*c*.

urine. Physical examination disclosed a well-nourished child with a large protuberant abdomen which deviated toward the right (fig. 1*a* and *b*). The upper portions of the rectus muscles were present, but the remaining abdominal muscles were absent. A mass considered to be an enlarged right kidney was

noted in the right flank in addition to a distended bladder. Bilateral cryptorchidism was present and slight dribbling of urine was noted.

Urinalysis revealed pyuria, grade 4, and an occasional red blood cell; micrococci were grown by culture. The value for urea was 44 mg. per 100 cc blood. Determination of residual urine disclosed 400 cc.

An excretory urogram revealed moderate dilatation of the pelvis and calyces of the right kidney and enormous dilatation of the right ureter (fig. 1*c*). There was no evidence of a functioning left kidney. A cystogram disclosed a huge vesical shadow which extended up to the fourth lumbar vertebra (fig. 1*d*). It was noted that the child remained dry for a period of 6 to 8 hours following removal of residual urine at which time urinary dribbling appeared.

A sound of 16F caliber was passed easily and cystoscopic examination disclosed a large atonic bladder which was not trabeculated. The base of the bladder appeared elevated and the interureteric ridge hypertrophied. Neither ureteral orifice was positively identified. The vesical neck particularly in the region of the floor appeared obstructive. Consequently a transurethral resection of the vesical neck was carried out in May 1945, utilizing a perineal urethrostomy. Three grams of tissue were removed and microscopic study of this tissue revealed hyperplasia of muscle and inflammatory reaction.

After removal of the catheter improvement in the size of the stream was noted, but urgency was present. A suitable corset was fashioned for the patient. At the time of dismissal the amount of residual urine was 125 cc. Determinations of residual urine were made regularly and urinary antiseptic agents were administered intermittently at home. The amount of residual urine gradually fell to an ounce or less and urination improved considerably; urinary leakage practically ceased.

Improvement continued, and at our request the patient returned for reexamination in February 1946. At that time vesical function was almost normal. The escape of a few drops of urine was noted when he was excited or engaged in strenuous exercise; there was no leakage of urine at night. Urinalysis disclosed pyuria, grade 1, and the urea content of the blood was 32 mg. per 100 cc. No residual urine was present and a 16F sound passed easily. By excretory urography it was noted that the pyelocaliectasis of the right kidney had appreciably decreased, although the tremendous dilatation of the right ureter remained unchanged. There was no excretion of contrast medium by the left kidney.

The child returned for his yearly examination in June 1947, at which time his mother stated that urination was normal; dribbling of urine was avoided by having the child void at regular intervals. During the past 16 months the child had experienced four attacks of chills and fever associated with cloudy urine which responded promptly to treatment with penicillin. Urinalysis disclosed pyuria, grade 3, and an occasional erythrocyte. Streptococcus faecalis was obtained by culture of the urine, and the amount of residual urine was 10 cc. The improved appearance of the right kidney was maintained as shown by excretory urography. The use of urinary antiseptics was advised and the patient was dismissed.

The patient returned in November 1948, for re-examination. His mother stated that the attacks of chills and fever occurred with greater frequency and that he complained of pain in the right lower quadrant of the abdomen during these attacks. Urinary control was excellent and the urinary stream normal. A firm, nontender mass, 3 cm. in diameter, was palpable in the right lower quadrant of the abdomen.

Urinalysis revealed pyuria, grade 3, and hematuria, grade 1; the appearance of the right kidney and ureter was unchanged as shown by excretory urography. Cystoscopy disclosed the prostatic urethra and vesical neck to be open widely; attempts at catheterization of the right ureter were unsuccessful.

It could not be determined whether the patient's symptoms and the small abdominal mass were related to the dilated right ureter or possibly epididymitis in association with the undescended right testicle. In view of the patient's good general condition surgical intervention was considered inadvisable and the patient was dismissed and advised to receive intermittent chemotherapy.

The patient returned for his annual examination in July 1950. He had experienced no further bouts of infection since the time of his last examination; his general health was excellent and he had no urinary symptoms. The small abdominal mass noted previously was no longer palpable.

Urinalysis yielded negative results and the urine was sterile; 35 cc of residual urine were found. Excretory urography revealed no change in the upper part of the urinary tract. The patient was dismissed and advised to return in one year.

The patient returned in March 1951, with no complaints or urinary symptoms. In the interim since his last examination he had experienced one attack of chills and fever, pain in the right renal region and dysuria which responded to treatment with penicillin. The patient's mother believed that the caliber of the urinary stream was decreased since that attack.

Urinalysis yielded negative results and the urine was sterile; 20 cc of residual urine were noted. The upper part of the urinary tract appeared unchanged as shown by excretory urography (fig. 1*e*). Cystoscopy revealed slight narrowing of the external urethral meatus and meatotomy was performed. Sounds up to 18F in size were passed easily and the bladder appeared normal except for hypertrophy of the interureteric ridge. The vesical neck was open widely.

The meatotomy and urethral dilatation resulted in considerable increase in caliber of the urinary stream and the patient was dismissed and advised to return in 1 year.

Comment on case 1:—This patient has been observed for a sufficient length of time to permit evaluation of therapy. It is our belief that resection of the vesical neck halted the progressive destruction of the upper part of the urinary tract and prevented death due to uremia. For the past year the patient has been asymptomatic, his urine has remained normal, there has been no residual urine and good renal function has been maintained. Mild pyelocaliectasis of the right kidney and enormous dilatation of the ureter persist, but there has been no progression since resection of the vesical neck was performed—a period of 6

years. In view of his excellent health we prefer continued observation rather than plastic procedures on the ureter. We surmise that the left kidney is atrophic.

Case 2.—A boy, 6 years old, was brought to the clinic in April 1946, because of a large abdomen, which had been noted at birth, and recurrent urinary infections. The patient had been ill practically throughout infancy. He had experienced feeding problems, slow gain in weight, constipation and frequent mild to severe respiratory infections. Two years before admission he had recurrent attacks of fever, and a diagnosis of infection of the urinary tract had been made and chemotherapeutic drugs prescribed with but slight beneficial effects. The child's thirst appeared insatiable and his mother estimated that he drank a gallon of water daily. Vesical function was apparently normal.

Physical examination disclosed a funnel-shaped chest with flaring of the costal margins. The abdomen was large and protuberant and an absence of the lower half of the rectus and oblique abdominal musculature was noted (fig. 2*a* and *b*). The liver and spleen were readily palpable and bilateral cryptorchidism was noted.

FIG. 2 (case 2). *a* and *b*, Anteroposterior and lateral views of symmetric deformity of abdomen with midline crease.

Urinalysis disclosed pyuria, grade 4, and hematuria, grade 1; streptococci and micrococci were noted by culture. The value for urea was 56 mg. per 100 cc blood. The presence of 400 cc residual urine was determined. Excretory urography disclosed moderate dilatation of the pelvis and calyces of the right kidney; there was no evidence of a functioning left kidney (fig. 3*a*). A retrograde cystogram revealed a large, smooth sacculated vesical outline (fig. 3*b*). Definite hypertrophy of the posterior commissure of the prostate which resulted in a deep gutter between the verumontanum and vesical neck was noted by cystoscopic examination. The trigone appeared normal; the left ureter was catheterized and only an extremely dilated ureter was outlined by pyelography (fig. 3*c*).

In view of the severe recurrent infections of the urinary tract it was considered best to perform left nephro-ureterectomy first, and this was carried out in April 1946. The kidney was atrophic, and almost complete destruction of the parenchyma was noted. The redundant ureter was approximately equal in size to the child's colon. The kidney and ureter weighed 37 gm. and microscopic

study disclosed atrophy of the kidney. Convalescence was uneventful. An abdominal support was fitted and the patient was dismissed with instructions to return for further studies.

The child returned in June 1947. In general, his health had been good except that he appeared to tire easily and had poor appetite. He had had no urinary symptoms, but repeated urinalysis had revealed severe pyuria. Urinalysis at this visit disclosed pyuria, grade 4, and an occasional erythrocyte; culture of the urine was reported to be sterile, although many gram-positive cocci were noted. The urea content of the blood was 60 mg. per 100 cc and the residual

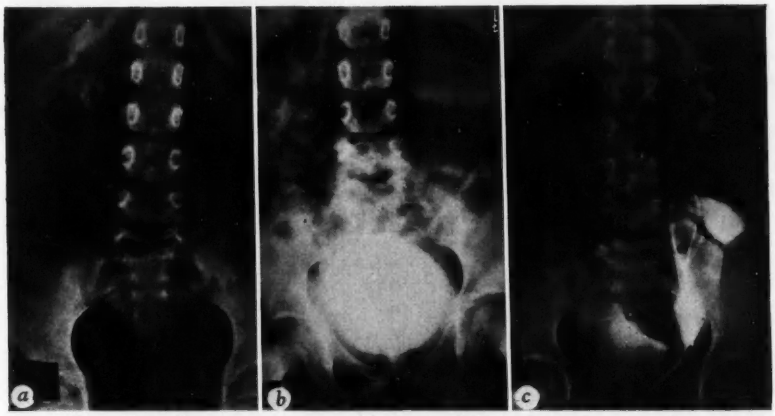

FIG. 3 (case 2). *a*, Excretory urogram. Moderate right hydronephrosis and nonfunctioning left kidney are noted. *b*, Retrograde cystogram. Enlarged vesical outline with sacculation is apparent. *c*, Left retrograde pyelogram. Extreme dilatation and tortuosity of left ureter are present.

urine measured 140 cc. The urographic appearance of the right kidney was unchanged.

In July 1947, resection of the vesical neck was performed with the infant resectoscope. Two grams of tissue were removed and microscopic examination of this tissue disclosed inflammatory muscle.

After resection the patient voided satisfactorily and the amount of residual urine decreased to 50 cc. The child was dismissed from our care and advised to receive intermittent chemotherapy and have monthly determinations of residual urine.

In response to inquiry in November 1947, the patient's mother stated that the child was in good health and "from his actions one wouldn't know there was anything wrong." He had no urinary symptoms and the last determination of residual urine disclosed only 15 cc. Subsequent attempts to contact the patient have been unsuccessful.

Comment on case 2:—Recurrent severe infections of the urinary tract necessitated removal of the functionless left kidney. Resection of the vesical neck

was followed by a gratifying decrease in the amount of residual urine, and four months later the child was apparently entirely well. Unfortunately efforts to learn of the patient's further course have been futile.

Case 3.—A boy, 4 years old, was brought to the clinic in March 1947, because the mother had noted the appearance of swellings on each side of the child's

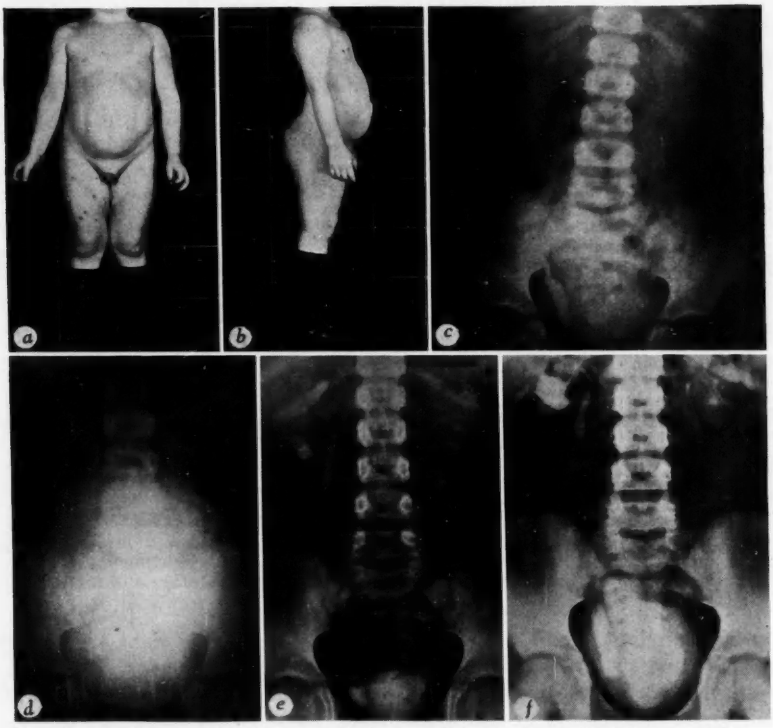

FIG. 4 (case 3). *a* and *b*, Anteroposterior and lateral views. Protuberant abdomen is somewhat masked by child's obesity. *c*, Excretory urogram made in 1947. Upper part of urinary tract is poorly visualized but lower right ureterectasis is well shown. *d*, Retrograde cystogram made in 1947. Extreme vesical dilatation is noted. *e*, Excretory urogram made in 1950. Striking decrease in size of vesical outline as compared with figure 4*d*. *f*, Excretory urogram made in 1951. Increased caliectasis of the right kidney as compared with figure 4*c*. Right ureterectasis is unchanged and vesical outline appears normal.

abdomen during exercise. Dribbling of urine both during the day and night was noted.

Physical examination disclosed a large obese boy, who was 20 pounds overweight. A marked bulge was noted in the left flank when the patient strained, and the skin over the abdomen appeared redundant in spite of the obesity (fig. 4*a* and *b*). A small ventral hernia was present above and to the right of the umbilicus and there appeared to be incomplete absence of all the lower abdominal muscles particularly on the left side. Bilateral cryptorchidism was present.

Urinalysis gave negative results and a culture of the urine was sterile. Excretory urography disclosed mild caliectasis on the right and marked irregular dilatation of the lower third of the right ureter; minimal dilatation of the calyces of the left kidney was present (fig. 4*c*). Two determinations of residual urine yielded 500 and 600 cc respectively. A retrograde cystogram showed a large, rounded, smooth vesical outline which extended up to the third lumbar vertebra (fig. 4*d*). Cystoscopy disclosed a large smooth bladder with considerable redundancy of the tissue of the trigone. The right ureteral orifice was gaping; the left appeared normal and catheterization of either ureter was impossible. No obvious obstruction at the vesical neck was noted.

It was decided to perform resection of the vesical neck because of the large amount of residual urine and the large flabby bladder. This operation was carried out through an external urethrotomy in April 1947, and 4 gm. of tissue from the vesical neck were excised. Microscopic examination of this tissue disclosed an inflammatory reaction in the muscle. Convalescence was delayed owing to drainage of urine through the perineal wound, but this soon ceased and the wound healed.

Prior to dismissal the patient was able to void a larger excellent stream and his mother stated that his abdomen no longer appeared distended. An abdominal support was fitted, chemotherapy was suggested and the child was dismissed with advice to return in three months.

The child was returned in August 1947, and the mother stated that he had been well during the interim. He was able to void an excellent stream, and involuntary dribbling of urine occurred only if he delayed urination and permitted his bladder to distend.

Urinalysis disclosed pyuria, grade 1, and no residual urine was found. An excretory urogram revealed the upper part of the urinary tract to be unchanged. The patient was dismissed and advised to return for re-examination in six months.

The patient returned in February 1948. His mother stated that his health had been good. His urinary stream was excellent in caliber and involuntary dribbling of urine occurred only at times when he wore the abdominal support and delayed urination for more than three hours. Urinalysis gave negative results and the urine was sterile. The urea content of the blood was 32 mg. per 100 cc. A 12F catheter was passed easily and no residual urine was found. The urographic appearance of the upper part of the urinary tract was unchanged. A retrograde cystogram showed considerable reduction in size of the vesical outline. The patient was dismissed and advised to return in two years.

The patient returned in April 1950. His mother stated that his urinary control had improved considerably; incontinence of urine occurred only rarely and at times of great activity. Urinalysis gave negative results and there was no residual urine. The urea content of the blood was 28 mg. per 100 cc. An excretory urogram revealed increased caliectasis of the right kidney; the right ureter and left kidney appeared unchanged (fig. 4*e*). The vesical outline was irregular but of normal size. Because of the increasing caliectasis it was advised that the child return in one year.

The patient returned in April 1951. The mother stated that during the past 6 months his urinary control had been excellent and he had experienced no urinary symptoms. Urinalysis gave negative results and there was no residual urine. The urea content of the blood was 40 mg. per 100 cc. Excretory urography disclosed increased caliectasis of the right kidney; the right ureter, left kidney and bladder appeared unchanged (fig. 4*f*). The child was dismissed and it was suggested that he return in one year, principally in order to permit study of the right kidney.

Comment on case 3:—This patient has been observed for 4 years. It is our belief that resection of the vesical neck has eradicated residual urine and urinary incontinence. The patient's health is excellent, but the increasing caliectasis of the right kidney is disconcerting. It is likely that this is due to ureteral reflux, and if the caliectasis continues to increase, re-implantation of the ureter into the bladder may be necessary.

Case 4.—A boy, 2½ years old, was first seen elsewhere in February 1948, because of constant drainage of urine through an opening in the lower part of the abdomen; the child had never voided through the penis. He had not walked because of a deformity of the right foot. He had not started to talk but made peculiar noises which sounded like attempts at talking. His abdomen was large and protuberant and he was severely troubled with constipation.

Physical examination disclosed normal vocal cords. The abdomen was protuberant and flabby and the lower parts of the rectus, oblique and transverse abdominal muscles were absent (fig. 5*a* and *b*). The peritoneal contents were easily palpable through the thin abdominal wall. The bladder was distended, and pressure over the vesical area resulted in a discharge of urine from a patent urachus 5 mm. in diameter. Bilateral cryptorchidism was present. Although the penis was well developed, the external urethral meatus was represented by a shallow recess and the corpus spongiosum could not be palpated; the prostate gland was not palpable. The right foot consisted of a heel with attached toes. Merrill-Palmer tests revealed that the child's mental age was 3 years.

Urinalysis disclosed pyuria, grade 1, and cultures of the urine were sterile. Nonprotein nitrogen in the blood measured 50 mg. per 100 cc. Visualization of the upper part of the urinary tract by excretory urography was unsatisfactory owing to gas in the bowel; it was possible to determine only that two kidneys were present.

The recess in the tip of the glans penis was probed but no opening was detected. A catheter was passed through the patent urachus and a cystogram disclosed an irregularly dilated bladder which, in lateral view, appeared attached to the anterior abdominal wall (fig. 5*c* and *d*). Cystoscopy through the patent urachus revealed slight trabeculation of the bladder and a well-formed trigone; attempted catheterization of the ureters was unsuccessful. The vesical neck was represented by a depression which ended blindly.

Bilateral ureterosigmoidostomy was considered the procedure of choice and was carried out in March 1948. Both ureters appeared dilated and the bladder

large. Three days after operation the nonprotein nitrogen content of the blood dropped to 29 mg. per 100 cc. Convalescence was uneventful and the postoperative urogram, in which structures were still obscured by gas, disclosed greater concentration of medium in the kidneys. An abdominal corset and a prosthesis for the foot were obtained and the child was dismissed. Ten days after dismissal the patient experienced an attack of acute pyelonephritis which subsided rapidly after chemotherapy, and he was again dismissed.

His condition remained good for approximately one year, but thereafter slow, gradual deterioration developed. He was readmitted to the hospital in July 1949, in a state of coma; the nonprotein nitrogen content of the blood was 195

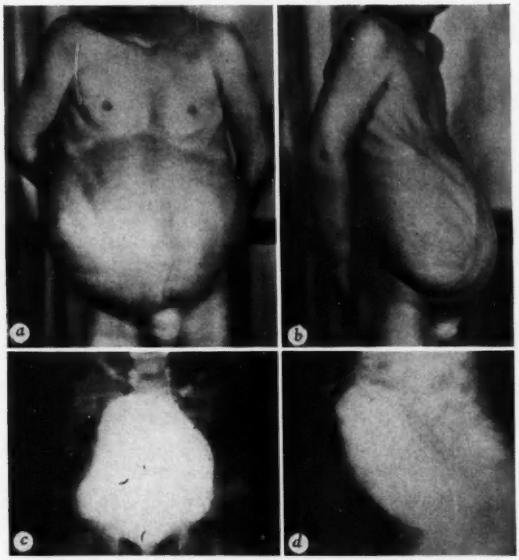

FIG. 5 (case 4). *a* and *b*, Anteroposterior and lateral views. Slight asymmetric enlargement of abdomen. *c*, Cystogram, anteroposterior view. Irregular outline of the dilated bladder is shown. *d*, Cystogram, lateral view. Bladder appears attached to anterior abdominal wall by patent urachus.

mg. per 100 cc. Therapy was futile and the patient died two days after admission; permission for necropsy was refused.

Comment on Case 4:—The profound abnormalities present in this case precluded any therapy other than diversion of the urinary stream by ureterosigmoidostomy. Atresia of the urethra is the extreme example of infravesical obstruction resulting in distention of the bladder and subsequent hydronephrosis and hydro-ureter.

The patient in this case was treated by one of us (Culp) at the Henry Ford Hospital, Detroit, and has been included in this series through the courtesy of Dr. John K. Ormond, Chief of the Division of Urology of that institution.

Case 5.—A male infant, 5 months old, was brought to the clinic in April 1951, because of recurrent attacks of fever associated with diarrhea and constipation. Urinary symptoms had not been noted. The abdominal muscles were absent at birth.

The pertinent findings noted at physical examination were absence of the lower portions of the rectus, oblique and transverse abdominal muscles and bilateral cryptorchidism (fig. 6*a* and *b*). Intestinal movements were clearly visible; the right kidney was palpable and the bladder was distended.

Urinalysis revealed mild pyuria and culture of the urine disclosed numerous organisms (Streptococcus faecalis). The urea content was 80 mg. per 100 cc blood. Roentgenographic study of the colon revealed no abnormality. By means of excretory urography it was determined that both kidneys were functioning, but further interpretation was impossible. An unsuccessful attempt was made to determine the amount of residual urine; the largest catheter that could be passed through the urethra was a 6F ureteral catheter, and the drainage was unsatisfactory. A retrograde cystogram disclosed a large pyramid-shaped vesical outline. Both ureters were outlined and appeared markedly dilated and tortu-

FIG. 6 (case 5). *a* and *b*, Anteroposterior and lateral views. Slightly asymmetric protuberant lower part of abdomen is evident. *c*, Retrograde cystogram. Dilatation of bladder with reflux resulting in visualization of bilateral hydro-ureters.

ous; the right kidney was visualized incompletely but extreme hydronephrosis was noted (fig. 6*c*).

Cystoscopic examination disclosed a large trabeculated bladder and a constricting band of tissue extending across the posterior vesical neck from the 5 to 7 o'clock positions. The prostatic urethra and verumontanum appeared normal. The constricting band was obliterated by multiple linear incisions, and a 12F catheter was placed indwelling.

Following removal of the urethral catheter the urinary stream was excellent and the amount of residual urine was only 3 cc. The bladder was palpable as a small contracted mass. An abdominal corset was fitted and the infant was dismissed. It was advised that intermittent urinary antisepsis be employed and that the infant be returned in 3 months for re-examination.

Comment on case 5:—The immediate results of operation, namely, relief of vesical distention and eradication of residual urine, have been encouraging. However, the moderate azotemia and profound pathologic changes in the upper part of the urinary tract are ominous signs which will require further observation.

COMMENT

The abnormality of the urinary tract which was present in all cases of congenital absence or deficiency of abdominal musculature which we observed was distention of the bladder with an appreciable amount of residual urine. The changes noted in the upper part of the urinary tract were hydronephrosis and hydro-ureters of varying degree, and atrophy of the kidney. All patients were male and they had bilateral cryptorchidism.

It is our opinion that the primary pathologic problem is obstruction at the vesical neck which results in distention of the bladder and the presence of residual urine. The changes in the upper part of the urinary tract result as a consequence of the vesical distention. Thus we are in agreement with Stumme and Housden in our belief that the obstruction of the neck of the bladder occurring in utero results in distention of the bladder and atrophy of the lower abdominal muscles due to pressure by the distended bladder. The use of a snugly fitting corset or abdominal binder is an important aid in raising intra-abdominal tension to permit more effective evacuation of the urinary bladder.

It is our opinion that in patients in whom fair or good renal function is present, efforts should be directed toward relieving the primary cause of the disability, namely, the obstruction at the vesical neck. The patient's ability to void a good stream and the physician's ability to pass a urethral catheter does not preclude the presence of obstruction at the vesical neck. An absence of, or failure of the mother to note, urinary symptoms does not imply that distention of the bladder is absent. Determinations of the amount of residual urine, an important diagnostic test, are practically lacking in the cases described in the literature.

Furthermore, obstructions at the vesical neck may be difficult or impossible to appreciate even by cystoscopic examination. Actual resection of the vesical neck may be necessary to determine whether obstruction is present. If such resection results in a striking decrease in the size of the bladder and disappearance of residual urine, it may be safely assumed that obstruction of the vesical neck was present originally. Just such observations were made in the 4 cases in our series in which this procedure was possible. The relief of vesical distention and residual urine permitted eradication of infection and prevented further progressive deterioration of the upper part of the urinary tract. This part of the urinary tract is usually so profoundly altered that one cannot expect the kidneys and ureters to return to normal, even after the vesical distention has been relieved, and one must be satisfied with the existing condition.

It is obvious that some patients afflicted with this condition, when first seen, will exhibit such profound deterioration of renal function that nothing less than lifesaving nephrostomy or nephrectomy will be suitable. It is our opinion, however, that many operations such as ureteroplasty and ureterovesical reimplantation, which have been employed in this condition, deal with an effect rather than a cause.

Our appreciation is expressed to Miss Lucia Warren of Spencer, Incorporated, for her invaluable aid in designing the corsets used in these cases.

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VESICOSIGMOIDOSTOMY FOR EXSTROPHY OF THE BLADDER

SAMUEL A. VEST AND (by invitation) WILLIAM H. BOYCE

From the Department of Urology, University of Virginia Hospital, Charlottesville, Va.

Exstrophy of the bladder has presented a constant challenge to the urological surgeon. Over the last century the large number of procedures which have been devised for the correction of this distressing anomaly attest to the unsatisfactory therapeutic state. Admittedly, the most ideal procedure is reconstruction of the bladder and vesical sphincters without diversion of the urinary stream but in the vast majority of instances such plastic reconstructive surgery is unsuccessful and impractical, resulting in permanent fistulas at the base of the penis, or else a persistence of incontinence because of an inadequate sphincteric mechanism. Furthermore, perivesical adhesion and the small size of the bony pelvis often preclude the development of a functional bladder of adequate capacity. With consistent failure along reconstructive lines, some form of diversion of the urinary stream has been the only recourse. A large number of varied technical procedures have been devised for diversion of the urinary stream in this benign condition.

Whether the commonly used ureterosigmoidostomy has led to an increased expectancy of life in this condition is indeed open to question as there are no acceptable statistics on longevity in the untreated patient. Charles H. Mayo in 1925 stated that 50 per cent of untreated patients with exstrophy of the bladder are dead by the tenth year and 66.67 per cent dead by the twentieth year. Unfortunately, he did not give any proof or source for these figures. Harvard and Thompson of the Mayo Clinic recently traced 98 patients in whom the Coffey principle of uretero-intestinal anastomosis had been utilized for exstrophy and when compared to Mayo's statement concluded that an increase in survival rates definitely occurred following this type of urinary stream diversion. Whether transplantation has actually increased life expectancy or not has been of secondary importance to the improvement in the state of affairs which follows the institution of urinary continence in these unfortunate individuals. They are rehabilitated from a social standpoint and this objective is probably more important than the unsatisfactory aspects of uretero-intestinal anastomosis.

A critical analysis of the reported cases following uretero-intestinal anastomosis leaves much to be desired. The long term results following all methods of ureteral transplantation are not good. No technique has yet been perfected which is not accompanied by the hazards of late pyelonephritis or obstruction to the upper urinary tract as a result of cicatricial changes. As an example, Harvard and Thompson in their recent survey following the Coffey technique of transplantation for exstrophy, state that 50 per cent of immediate postoperative deaths were due to pyelonephritis; 79 per cent of known causes of death after the patients left the hospital were due to uremia; and 69.4 per cent of the survivors gave a history of pyelonephritis. In 41 postoperative excretory

urograms 34 per cent of which were made less than one year after operation, there were only 5 per cent which could be considered normal. Even in the latter (5 per cent) with normal pyelograms, one cannot say that low grade pyelonephritis is absent and that it will not become more manifest at a later date resulting in a greater rate of renal destruction. As evidence of this, in our own experience, in 1946 it was realized soon after ureterosigmoidostomy in a child that we had effected an excellent anastomosis on the left side in which the kidney appeared normal in an excretory urogram but with obstruction on the right. At a later date, we re-operated and re-implanted the right ureter. The patient returned the other day, and after an absence of 5 years we found that the previously "normal" left side now showed evidences of hydronephrosis while the excretory urogram on the re-implanted and once obstructed right side was entirely normal at this date. Nevertheless, the burden of proof would certainly rest on anyone who assumed that pyelonephritis did not exist in this right kidney in spite of the normal urogram. It certainly must exist in all patients following transplantation in which there is any dilatation or urinary stasis.

The technique of ureteral transplantation has been improved over each decade and the use of antibiotics has been invaluable. They have undoubtedly reduced the immediate mortality and infection at the site of anastomosis with also a reduction of scar tissue and late obstruction. The late results with modern technique and antibiotics are yet to be ascertained but it is doubtful that ureterointestinal anastomosis in childhood will ever offer any patient a normal expectancy of life. They die of late obstruction and infection with each complementing and accentuating the other. One cannot deny, however, that there is something intangible about transplantation of the ureter because one encounters a rare case which does not seem to develop evidence of pyelonephritis or obstruction, and the patient seems to be progressing through each 5 year period without evidence of renal deterioration. Unfortunately, such cases are far too few and no statistics have been presented to date in transplantation for exstrophy of the bladder that would in any way lead one to assume or conclude that a patient would have a normal expectancy of life. It therefore occurred to us that the previous surgical techniques should be re-studied to see if some improvement or variation would not offer the patient with exstrophy a normal or at least a much longer expectancy of life than is hitherto possible by present or previous methods. Since morbidity and late mortality following ureterosigmoid transplantation have been striking features of previous techniques it seemed to us that some distinct variation in technique would be in order. We concluded that the common denominator which finally ends in progressive renal insufficiency directly following obstruction and infection must be disturbance of the terminal ureters. An ideal operation, therefore, should not mobilize or disturb the lower ureters at any point. Maydl and Bergenhem made some attempt at this by transplanting either the trigone or terminal ureters with a cuff of bladder mucosa. In this, they sought to preserve the ureterovesical valves and undisturbed ureteral orifices. We are not convinced from experience that their procedures are sound, because the terminal ureters

must be mobilized and somewhat angulated as they are turned downward for implantation into the anterior surface of the rectum.

In order for the patient to have a normal life expectancy, the ideal operation must leave wholly undisturbed the entire ureters including those portions which traverse the bladder wall. At the same time, utilization of the rectal sphincter is imperative for continence of urine. With this concept in mind, we have devised the following procedure and would like to report today its successful use.

CASE REPORT

An intelligent 9 year old boy was admitted to the University of Virginia Hospital in July 1950, with a congenital exstrophy of the bladder. Excretory urograms showed normal kidneys and ureters, and there was no history to indicate previous pyelonephritis. A preliminary colostomy was performed and the lower sigmoid sterilized insofar as possible by means of instillations of antibiotics (sulfasuxidine, sulfathalidine, aureomycin, streptomycin, and penicillin). Ten days after the colostomy and partial sterilization of the lower sigmoid the second stage of the procedure was then performed as follows. A vertical midline incision was made through the entire trigone leaving the terminal ureters and ureteral orifices entirely undisturbed. This incision was carried down through the entire bladder wall and cul-de-sac of the peritoneum, exposing the anterior surface of the rectum. The upper margin of the bladder incision was sutured to the peritoneum covering the anterior rectal wall so as to close the opening into the peritoneal cavity and thus extraperitonealize the incision. A similar longitudinal incision was then made into and through the rectal wall just beneath the divided trigone. An anastomosis of these two openings was made by through and through suture of catgut, much in the manner of a gastro-enterostomy. This produced a mucosa-to-mucosa type of vesicorectal fistula or communication. In such a midline procedure, there was no disturbance whatever of the terminal or intramural ureters or the ureteral orifices. With a permanent type communication thus established between the rectum and the trigone, the operator then proceeded to excise the remainder of the urinary bladder except for that portion surrounding the newly-constructed fistulous opening and the ureteral orifices. This remaining portion was closed over anteriorly with a continuous suture of catgut, so that the bladder actually became a small "diverticulum" or "pouch" on the anterior surface of the rectum. In the lateral aspect of this "pouch" the normal orifices of the undisturbed ureters terminated. The "pouch" or bladder was approximately one ounce in capacity. The abdominal wall defect over this miniature bladder was next closed by approximating the fascia of the rectus muscle. The epispadic penis was then repaired. A Denis Browne type of urethra was constructed back to include the region of the prostatic urethra so that ejaculation might occur.

Convalescence was uneventful, and there was no elevation of temperature or evidence of pyelonephritis. During the operative period and immediately following the patient received penicillin and streptomycin. After removal of

a rectal tube, which allowed continual evacuation of urine from the rectum, the patient was given terramycin for several days. Within 2 months following the operative procedure, we were able to obtain sterile weekly cultures from

TABLE 1. *Cultures from isolated rectum*

DATE	CULTURE
8-5-50	Operation—Formation of rectal pouch
8-9-50	B. coli
	B. aerogenes
8-12-50	Staph. aureus hemolyticus
	Staph. albus nonhemolyticus
8-14-50	Sterile
8-15-50	Operation—Vesicorectal anastomosis; closure of bladder
8-18-50	B. coli
	B. aerogenes
8-21-50	B. coli
	B. aerogenes
10-2-50	Sterile
	Antibiotics discontinued
10-16-50	Sterile
10-23-50	Sterile
11-13-50	Sterile

TABLE 2. *Blood urea and electrolyte concentration before operation and after formation of trigono-rectal pouch*

DATE	BLOOD UREA	PLASMA CHLORIDE mEq./l.	PLASMA CO_2 mEq./l.
7-31-50	39	98.4	22.6
8-5-50	Operation—Formation of rectal pouch		
8-14-50	27		23.9
8-15-50	Operation—Vesicorectal anastomosis; closure of bladder		
8-18-50	29	93.2	
8-21-50	24	103.5	24.8
8-28-50	32	96.5	23.2
9-4-50	20	101.2	22.6
9-18-50	26	99.7	24.4
10-2-50	18	105.2	22.4
10-30-50	24	102.6	19.3
11-13-50	30	107.7	20.4
Normal Values:.....	25–35	97–106	23–27

the rectum for 4 weeks (table 1). Postoperative urograms were normal. The concentrations of blood urea, plasma chloride, and plasma carbon dioxide combining power remained within normal limits over 4 months, observation (table 2).

It was our intent at the inception of this procedure to use the colostomy

purely as a temporary diversion of the fecal stream as was suggested a number of years ago by others. We intended for the patient to return later for closure, but on discharge from the hospital the colostomy was functioning with only one movement a day. As a matter of fact, the colostomy functioned so perfectly with a single movement per day that the child handled the daily irrigations entirely alone and did not even have to wear a colostomy bag. The patient seems to be happy and does not wish the colostomy closed. With this we are entirely in accord because life expectancy with an evidently normal urinary tract, and especially with sterile urine, should equal that of any other child of his age. A minor evil (colostomy) has been substituted for a major one (exstrophy). If the colostomy were closed and the fecal stream again diverted to the rectum along with the urine, there would certainly then exist the hazard of pyelonephritis. Even if the colostomy is later closed, it is our belief that there will be less chance of pyelonephritis and obstruction to the upper urinary tract with the completely undisturbed terminal ureters than if conventional ureterosigmoidostomy had been employed.

SUMMARY

A technique has been reported which serves to divert the urinary stream to the rectosigmoid for the purpose of urinary control in exstrophy of the bladder. The cardinal feature of this procedure which is simply the construction of a permanent fistula between the trigone and rectum is that there is no disturbance whatever of the ureters at any point. It is hoped that as a result, late obstructive and cicatricial changes will not result and thus will be avoided the finally fatal, ascending infection which occurs almost uniformly in some form and to some degree after all methods of intestinal transplantation of the ureters. There is no evidence yet that transplantation of the ureters at any age in this condition leads to a normal expectancy of life, and the greatest hazard is pyelonephritis.

One cannot be sure from a single case, but from the cultures herein reported we can certainly entertain the idea of permanent sterilization of the urinary tract in such cases. If this is true, the maintenance of a permanent colostomy is certainly a lesser evil than the complications that might arise from ascending urinary tract infection if the fecal stream is again diverted in conjunction with that of the urine. If this concept proves to be correct and if the excellent results in this case can be consistently duplicated, then transplantation or any disturbance of the ureters in exstrophy of the bladder within the first few months of life, as is now advocated by many, merits serious re-evaluation. Any procedure undertaken must not doom the patient to a premature death or shorten life expectancy.

DISCUSSION

Dr. Edgar Burns (New Orleans, La.): I should like to discuss Dr. Senger's report.

(Slide) This is a schematic drawing of a case that we reported before this association in 1945. It will be noticed that the septum runs in the frontal plane. The ureters or ureter rather, since this child had congenital absence of the right kidney, emptied into the large posterior pouch and the urethra communicated with the smaller anterior pouch. The opening between the posterior and anterior pouch was too small to allow the posterior pouch to completely empty so that in effect, the child has the same clinical condition as if the obstruction had been at the bladder neck.

This child was seen at the age of nine months with the distended bladder and had been running chills and fever for a period of six months. The septum was removed and normal bladder function restored.

(Slide) In the months that followed, the child developed multiple stones in the solitary left kidney which were most likely based upon infection. Urograms showed a dilatation of the upper minor calyces. It was obvious that the stones should be removed, but it was felt that the dilated calyces in the upper pole would predispose the recurrence. For that reason, this portion of the kidney was resected.

(Slide) This slide shows the immediate postoperative result with the nephrostomy tube still in place. The child is now seven years old, has sterile urine and has grown normally.

(Slide) Within the past six months, we have seen a second case, a male aged two and one-half years. It will be noted that the septum runs in the saggital plane. The urethra communicates with the right side of the sacculated bladder. Two openings through the septum can be seen in the cystogram. The bladder outline is typical of this type of case. The septum was removed, and the child has done quite well since. He has gained weight, but we have had inadequate follow-ups for the reason that he has been operated upon within the last six months.

I should like to say a word regarding the cases presented by Dr. Greene. We saw a boy aged $1\frac{1}{2}$ years with an absence of the musculature of the anterior abdominal wall. This child was typical of the ones he presented. In the addition of absence of muscles in the abdominal wall, he had bilateral cryptorchidism, bladder neck obstruction and a markedly dilated upper urinary tract. The obstruction was removed and normal bladder function restored.

Dr. George F. Cahill (New York, N. Y.): Six cases such as discussed by Dr. Greene were reported from Babies Hospital, New York. After these cases were assembled we believed the condition to be more frequent than their appearance in the literature. Although the popular theory is that the changes are due to vesical neck obstruction, they are not clearly all due to that because we see comparable obstructions without the muscle atrophy of the abdominal wall and other abnormalities, and in these cases there is at times no evidence of abdominal muscles being present at all.

By the time a diagnosis is made, simple relief of the bladder neck may not suffice to correct all the obstructions occurring then, and may require correction of secondary higher obstructions. As yet to my knowledge there has been no correction of the muscle wall failure reported by general surgeons. The child develops a compensatory movement mechanism which takes care of the deficiency as shown so well in the film by Dr. Greene.

Dr. Reed M. Nesbit (Ann Arbor, Mich.): I would like to make inquiry of Dr. Greene and also of Dr. Burns, as to whether the abdominal musculature has shown any return of function following the successful treatment of the obstruction in these cases.

Dr. Gershom J. Thompson (Rochester, Minn.): Eight of the cases Dr. Greene reported were reported out of Babies' Hospital, from the Urologic Department which I happen to head. We believe this condition is much more frequent than people realize or recognize. In fact, when we went over this thing ourselves, we found we had two cases in which the thing actually, as far as the syndrome itself was concerned, was not recognized completely in the beginning. We have had several cases since the report was made.

In studying the theory, it is difficult to concede that the whole thing is based upon obstruction of the neck of the bladder because we see just as marked bladder neck obstruction occurring in children without musculature atrophy or the other anomalies which go far beyond bladder neck obstruction. They fail to suggest that one of the things may have been that it was an anomalous failure of blood supply distribution associated with the muscular atrophy of the wall, or the failure of the musculature of the wall to form. The failure to function of one kidney, which seems to be frequent, may be hydronephrotic or hydroplastic. That has occurred.

I do not think the treatment of these cases is quite as simple as a bladder neck obstruction by itself. Relief is not going to correct them all. Most likely, a series of reliefs will be necessary.

In our experience, some of them were so bad, the first thing we did was a bilateral nephrostomy so we could save their lives. Then we proceeded to remove the bladder neck obstruction, having the drainage at the highest possible level.

What has been shown by some of these cases is that it is easy, by relieving bladder neck obstruction alone, for the child to show marked improvement subsequently. I have seen no effect yet on these children by the abdominal surgeon's attempt to do anything to the muscular atrophy which they have presented. They have not touched any of the children we have.

The child develops a compensatory movement mechanism which takes care of the deficiency. The film showed how they compensate when they get up from the floor. They use other muscles because the abdominal muscles are of no help to them.

Dr. Meredith Campbell (New York, N. Y.): It was my fortune to see two cases of this type in Bellevue Hospital, and contrary to statistical data, these were both girls. The striking thing about these patients was not only the distended bladder, in both cases associated with rather pronounced lumbosacral

spinal defects and obvious cord involvement, but the paper thinness of the abdominal wall. It was like feeling the abdominal contents through a handkerchief. The bowel could be picked up in the hand, or the hand gotten around the bladder. It is a most interesting syndrome and a rare one.

Dr. John L. Emmett (Closing): To answer Dr. Nesbit's question, we have not observed any return of tone of the abdominal musculature following transurethral resection in any of our cases.

There are, I believe, still some questions in your minds about this subject. One no doubt is whether or not there is adequate proof that obstruction of the vesical neck actually exists, as most reports in the literature have failed to mention its existence. The reason for this is no doubt the fact that most of these are necropsy examinations. If the pathologist does not see a gross obstructive lesion, he infers that none is present. Such an examination is not adequate. Obstruction at the vesical neck in an infant is difficult to find, even if one is experienced in looking for it; it usually consists of mild varieties of contraction or "redundancy" of the vesical neck, or small collars, which can be adequately seen only with cystoscopic examination. Also, as we have stated many times, a normal vesical neck can be obstructive in the presence of an atonic bladder.

The final and convincing evidence that obstruction exists, however, is the fact that we now have four consecutive cases in which by transurethral resection of the vesical neck we have eliminated the residual urine, maintained urinary control and have apparently stopped progressive obstruction in the upper urinary tract.

There are one or two interesting points in surgical technique which might be mentioned here. The first is the use of the perineal approach to introduce the resectoscope. In male infants one must be exceedingly careful not to leave the child with a stricture at the penoscrotal junction from the passage of too large instruments. This procedure was first suggested for use in infants by Nesbit and I am not sure that it has been sufficiently publicized. The infant McCarthy resectoscope is 16F. The infant Thompson punch, which we use almost exclusively, is 18F. If one considers the beak on the punch, it is even larger. If a No. 20 sound will not pass easily, I always use the perineal approach. I have recently used this approach satisfactorily in a twelve-month-old baby boy. A No. 22 sound passed easily through the perineal incision, through the bulbous urethra, and into the bladder. I assume that such a procedure could be successfully done in infants much younger.

Another procedure I have found extremely helpful is to introduce a fairly large (18 to 22F) bag catheter through the perineal wound into the bladder for postoperative drainage, rather than struggling with a small catheter through the penile urethra. In case of postoperative bleeding, it furnishes much better facilities for irrigation and drainage. This method will in no way compromise the results of operation. There is no hurry about closing the perineal wound. As a matter of fact, it is often advantageous to make a second cystoscopic examination four or five days later through the perineal wound, to see if more tissue should be removed. It is always much easier to cut and remove tissue at a second sitting,

after the blood supply has been interfered with previously. Also, it is often remarkable how much better resection is done at the second sitting, even though the first seemed adequate at the time. At any time after the second procedure a small catheter can be inserted through the penile urethra and the wound allowed to close, with or without a suture in the urethra. By this time it will close from the bottom to the outside, avoiding subcutaneous abscess formation.

One more trick may be worth mentioning. The last case shown by Dr. Greene was a five-month-old baby boy. It was our impression on cystoscopy (with the 13F McCarthy infant cystoscope) that the obstruction was entirely caused by a small bar. To avoid a perineal incision (which would have been necessary for the introduction of a resectoscope) we cut off the bead tip and scraped away the insulation from the tip of a flexible 5F Bugbee electrode, leaving about $\frac{1}{4}$ inch of bare copper wire. The electrode was then introduced through the scope and multiple linear incisions were made with the bare wire across the bar, using the cutting high frequency current. The procedure was apparently successful.

EVALUATION OF OPERATIONS FOR HYPOSPADIAS

EDGAR BURNS AND GEORGE E. BECKMAN, JR.

From the Departments of Urology, Ochsner Clinic and Tulane University of Louisiana, School of Medicine, New Orleans, La.

Hypospadias is a common developmental anomaly of the male external genitals. It is characterized by 1) ventral incurvation of the penis, produced by bands of fibrous tissue occupying the position of the undeveloped corpus spongiosum and 2) an ectopic urethral meatus, which may be located at any point on the undersurface of the penis from the perineum to a position just back of its normal location in the glans penis. Treatment, therefore, consists in first correction of the penile deformity and later construction of the urethra. In 70 per cent of cases the ectopic meatus is on the ventral surface of the glans at or just behind the coronal sulcus and no treatment is indicated except in the occasional case of a stenotic orifice, which should be dilated or incised. In the remaining 30 per cent there is a varying degree of ventral deformity which must be corrected by removal of all constricting bands as a preliminary to construction of the urethra at a later date.

THE STRAIGHTENING OPERATION

The straightening operation should be done when the child is between 18 months and 2 years of age if he is seen during that time. The reason given for performing the straightening operation early is that it affords the corpora cavernosa a better opportunity to develop. On the other hand, we have obtained a perfectly straight penis with normal sexual function when the operation was done on patients up to the age of 32 years. This is not offered as a reason for delaying the operation but to point out that good results can be obtained at any age. It should be emphasized that correction of the chordee is equally as important as construction of the urethra. Unless this is successfully done, sexual function will be impaired or rendered impossible.

The operation is relatively simple but meticulous attention must be directed toward removal of all fibrous bands that may be contributing to the chordee. Some of these lie lateral to the midline; many are flat and almost transparent and consequently easy to overlook; and some are located in the intracavernous septum.

This operation may be done by either of two methods. The first utilizes the Heineke-Mikulicz principle first used by Duplay in 1874 in which a transverse incision is made across the ventral surface of the penis just proximal to the glans and carried well into the prepuce on either side. Traction on the penis exaggerates the constricting bands so that they are easier to identify and remove. Buck's fascia and the intracavernous septum may be incised but injury to the corpora cavernosa is to be avoided. The wound is closed longitudinally.

The second method was first described by Edmunds and later by Blair; more recently it has been modified by Nesbit. It is especially applicable to the occasional case in which the fibrosis may involve the skin on the ventral surface of

the penis requiring its removal. In such cases the prepuce is freed, button-holed and swung over to cover the ventral defect. Attachment of the penis to the abdomen for a week or ten days, as advocated by some, is probably not necessary if all fibrous bands have been removed. Neither is diversion of the urinary stream indicated in connection with the straightening procedure.

CONSTRUCTION OF THE URETHRA

The question always arises as to how much time should elapse between the straightening operation and construction of the urethra. If the straightening operation is done in patients between the ages of 18 months and 2 years, it has been our recent custom to construct the urethra when the child is 4 or 5 years old. The small size of the penis in some children may necessitate a longer delay. In the older age group we believe that at least a year should elapse between the straightening procedure and final repair. It has been shown, and we have demonstrated in some of our own cases, that about a year is required for the scar tissue incident to the first operation to become soft and elastic and for the maximum blood supply of the tissue in this area to develop.

Diversion of the urinary stream. It is our belief that the urinary stream should be diverted regardless of the method used to construct the urethra. Perineal ureterostomy, in our opinion, is preferable to suprapubic cystostomy. However, in an occasional patient with perineal hypospadias there may not be enough room between the triangular ligament and the ectopic meatus to permit insertion of a perineal tube and in such cases suprapubic cystostomy would be the only method. The method described by Denis Browne and Cecil is certainly simple. After the perineal catheter has served its purpose and is removed, the fistula closes within 24 to 48 hours frequently with no leakage of urine whatsoever.

Techniques for construction of the urethra. A satisfactory method for construction of the urethra should fulfill the following requirements. First, it should be applicable to all degrees of the deformity; secondly, the urethra should be free from hairs and of approximately normal size and elasticity; thirdly, the operation should be capable of completion by the time the child first goes to school; fourthly, it should be simple enough for consistent performance by any reasonably capable surgeon and finally, it should conform to all the basic principles of plastic surgery.

A review of the literature reveals that no less than 148 surgeons claim originality in operations for repair of hypospadias. However, analysis of these operations indicates that they are all based upon five general principles. The first of these makes use of free grafts taken from extragenital sources, according to the method originally described by Nové-Josserand. Split thickness skin grafts are applied by a tunneling technique. The ureter, appendix, veins, vaginal mucosa and bladder mucosa have all been substituted for skin and to each of these procedures the name of the operator has been attached. The necessity for precision in preparing the graft, the difficulty of insertion and fixation, the problem of maintaining uniform pressure on the graft in apposition with the side walls of the tunnel and the accumulation of small blood clots provide the reasons for failure in enough cases to warrant discarding this method.

The second principle involves stretching the freed up urethra to the end of the penis according to the method of von Hacker-Beck. This operation is obviously confined to repair of minor degrees of hypospadias. Ritchie pointed out that in mobilization of the urethra into a single ended pedicle flap consideration must be given to maintenance of the blood supply. In addition to the possibility of slough, stretching the already short urethra may increase the ventral deformity and interfere with sexual function. We believe that this method should be discarded in favor of methods that better fulfill the requirements of the deformity.

The third principle is concerned with use of pedicle grafts from the penis or prepuce to build the urethra and use of penile skin to cover the defect.

a) In Cecil's adaptation of the Thiersch-Duplay principle for penoscrotal hypospadias the urinary stream is diverted by perineal ureterostomy and the operation is completed in one stage. In the case of perineal hypospadias, the urethra is constructed down to 1 cm. of the ectopic meatus. After healing is complete, the perineal opening is closed as a second step, according to the method of Duplay. The urinary stream is diverted by suprapubic cystostomy for the final repair. By this method the urethra is constructed entirely of hairless penile skin except in the perineal type. The flaps have a broad base and maintain an adequate blood supply. Staggering of the suture line decreases the frequency with which fistulas occur. The new meatus is at the level of the coronal sulcus. Excellent results are reported in the majority of patients operated upon by this method.

b) One of the first examples of a tube graft was described by Rochet. The tube was made from scrotal skin with its attached base proximal to the ectopic meatus. The tube was then drawn through a prepared tunnel to the tip of the glans penis. The new urethra has the obvious objection of being constructed of hair-bearing skin.

c) The method of D. M. Davis utilizes a tube graft made from the skin on the dorsum of the penis. The penis is bent dorsally so that the entire length of the tube can be utilized. A tunnel is made through the glans to the ventral surface of the penis and enlarged until the tube can easily be drawn through it and extended directly to the free end of the ectopic meatus. The dorsal end of the tube is freed in about two weeks if healing appears complete at that time. The meatus is situated at the apex of the glans. This method is not applicable to the more severe grades of hypospadias unless combined with some modification of the Thiersch procedure. Tunnels made through the glans penis have a tendency to contract and periodic dilations may be required.

A variation of this method is utilized in the Thompson-Russell operation in which the urethra is constructed from the prepuce and skin on the ventral surface of the penis. The base of the flap should be left broad in order to maintain an adequate blood supply. This method is not applicable to the more severe grades of the deformity. A considerable amount of penile skin on the ventral surface of the penis is utilized in forming the tube. The remaining amount of penile skin available to cover the defect without undue tension will further limit the usefulness of this method.

d) Ombrédanne's method, known as the sac operation, consists in formation

of the new urethra by gathering up the skin proximal and lateral to the ectopic meatus by means of a purse string suture. The defect is then covered with the prepuce, which is button-holed and brought over the glans. Although the cosmetic effect of this operation is not ideal, the functional result is highly successful. The new channel is seamless and fistulous formation is obviated. The disadvantage is that it is applicable only to the distal penile hypospadias.

The operation involving the fourth principle was first described by Bidder in 1892 and was slightly modified by Bucknall in 1907. It utilizes a combination of scrotal and penile pedicle flaps to construct the urethra. Bidder's operation consists in forming the urethra with both penile and scrotal skin, the former forming the roof of the urethra and the latter the floor. Parallel incisions are made on the ventral surface of the penis and extended for an equal distance on the scrotum. The flaps are dissected up for a short distance laterally so that they may be sutured. After the wound has entirely healed, the penis is liberated from the scrotum, carrying with it the newly formed urethra. The scrotal defect is easily covered with adjacent scrotal skin. This method is applicable only to penoscrotal hypospadias, and has the disadvantage of hair-bearing skin that forms the floor of the canal. However, it may be utilized after other plastic repairs have failed and there is inadequate penile skin to construct the canal.

In Cecil's modification of the Bidder-Bucknall operation the urethra is constructed from a nonhair-bearing area. This is applicable only in cases in which an adequate amount of penile skin is available.

e) Finally, the Denis Browne operation is based upon the principle of use of a strip of intact skin which acts as a nucleus from which epithelium grows to line the newly formed urethra. After the straightening operation has been performed, this operation is a one stage procedure which involves several distinct steps.

1) Perineal Ureterostomy: A Malecot catheter is inserted into the bladder on a sound; the sound is partially withdrawn and its curve reversed so that it points in the perineum. With a diathermy knife a short incision is made over the point until the catheter is exposed. It is then grasped with a forceps and its distal end drawn through the opening. Gentle traction is placed upon the catheter until its wings are felt against the internal sphincter. It is tested with an irrigating syringe to be sure that its position is such that the bladder will be kept completely empty. As soon as this has been determined, the catheter is fixed in position by sutures.

2) Two parallel incisions made along the ventral surface of the penis are brought together immediately behind the ectopic meatus. This outlines the strip of intact skin which constitutes the nucleus from which epithelium lines the tube. The width of this strip will vary with each individual case and its diameter should be approximately the diameter of the average urethra for that age group. A triangular area of epithelium is removed on either side of the glans penis.

3) Whole thickness flaps are dissected laterally for a sufficient distance to allow their approximation without tension. Bleeding encountered during this stage of the operation is chiefly oozing. Only obvious bleeders need be ligated and these with the finest possible catgut. Two stab wounds are then made in the scrotum, posterior and lateral to the posterior angle of the wound and the tissues

undermined to connect with the undersurface of the flaps. This permits escape of any serum that may accumulate under the flaps and no drainage material, tubes or rubber dams are necessary.

4) A complete dorsal slit is made from the base of the penis to the coronal sulcus and its edges are spread widely. This relaxing incision has a twofold purpose. It prevents any possibility of the slightest tension upon the flaps during closure and guards against any tension that might develop from edema during the early postoperative period. This incision is left open and epithelium covers this area in a surprisingly short time, usually by the end of ten days or two weeks.

5) The next step is approximation of the lateral flaps, which is accomplished by a double layer of sutures. The first layer consists of through and through silkworm gut or silver wire placed one half inch away from the edges of the skin flaps. The sutures are adjusted by use of plastic beads held in place by crushed aluminum bands and so placed that when locked there is one eighth of an inch play between the two margins of the flaps. Lead perforated shots may be substituted for the plastic beads and aluminum bands. The importance of accurately adjusting the sutures should be emphasized. A suture that is drawn too tightly may cause slough at that point; the point at which this is most likely to occur is, in our experience, the penoscrotal junction. The outer layer of sutures which approximates the skin margins is of the finest possible catgut. The sutures are interrupted and inserted with care so as to prevent inversion of the skin margins. The distal ends of the flaps are brought forward and attached by mattress sutures to the glans penis so that the raw undersurface of the flap is in apposition with the denuded area on either side of the glans penis. This places the new meatus in approximately a normal position.

No dressing is required unless there is a tendency to oozing from the undersurface of the flap in which case a pressure dressing may be applied for two or three hours.

The perineal urethrostomy tube is attached to a bedside bottle. The currently available antibiotics are used to prevent infection. The sutures may be removed as soon as healing appears complete, usually by the end of 10 to 12 days, and the urethrostomy tube may be removed at the same time. There may be some leakage of urine through the perineal wound during the first 24 to 48 hours but we have had no leakage after that period. The majority of these patients may be discharged from the hospital by the end of the second postoperative week.

Our experience with the Denis Browne operation has been extremely satisfactory. The scar tissue incident to the dissection on the ventral surface of the penis requires about a year to become soft and elastic. If the strip of intact skin is made of sufficient width, dilations are not necessary. The flaps have a broad base insuring an adequate blood supply and have no tendency to break down if the elementary rules of plastic surgery are observed. One of our patients had repeated bladder spasms and urinated through the newly formed canal during the first 48 hours without complicating or delaying the healing process.

In conclusion, it has been our experience that the Denis Browne operation is simple and easy to perform, is completed in one stage, requires a short period of

hospitalization, a factor of tremendous economic importance, and finally, is applicable to all degrees of hypospadias. For these reasons we believe it is one of the procedures of choice in the repair of this deformity.

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MODERN TREATMENT OF HYPOSPADIAS

ARTHUR B. CECIL

The modern treatment of hypospadias has been evolved over many years. There are no operations today that have not had their roots in the past. I do not intend to discuss this subject before this association in any didactic manner, but I hope that you will permit me to discuss some phases of the treatment of this deformity. I should first like to say something in regard to the treatment of certain cases of perineal hypospadias, as these present problems not only of today but of tomorrow.

When a baby is born, who from external examination it is impossible to say whether it is a case of perineal hypospadias or female pseudohermaphroditism, we as urologists have no more ability to determine its gonadal sex than has a midwife. At no age will any cystoscopic, endoscopic or x-ray examination be of any value whatsoever, nor are there at present any chemical or biological tests for the determination of sex; but this determination must be made and made at once, unless the parents are to take home a child that will wreak as much havoc as if they had taken home a mongolian idiot. From the very moment of birth there is no place in the world for an intersex individual. The first question is, "Is it a boy, or is it a girl?" Within a few hours the State must have a report, later the Church, and make no mistake about the determination of prying neighbors to wreak vengeance on the parents of such a baby. How is this determination to be made, and when is it to be made? It must be made on the day the baby is born or within the succeeding few days according to the baby's condition by exploratory operation. Coffey, in cases of exstrophy of the bladder, successfully performed uretero-intestinal implants before the mother ever saw the child. Babies stand anesthesia well. They are accustomed to anoxia.

Howard has pointed out that the greater the degree of hypospadias the greater the degree of feminism, and that in practically all cases of perineal hypospadias there will be present a vagina, uterus and tubes, so that sex is not to be determined by the finding of these organs but by gonads alone. Among the problems of today and of tomorrow are to determine whether the chromosomal content of intersex individuals is normal and as to whether it corresponds with the gonadal sex.

Since I have started on the discussion of perineal hypospadias, I shall continue with this discussion to the cure of this condition. We will assume that the penis has been straightened. It has been determined by a vaginogram that the child has a vagina, and the question comes up as to what to do with this vagina. From Howard's observation that a vagina was constantly present in perineal hypospadias, it occurred to me that since I had cured many cases of perineal hypospadias without removal of the vagina, that simply because I now knew of its presence was no reason for its excision as had been previously advocated. I, therefore, constructed the urethra from the opening of the urogenital sinus to the end of the penis, thus throwing the vagina to empty into the urethra

instead of excising it. I am sure that this is the best method for dealing with the vagina in cases of perineal hypospadias.

I will briefly discuss the treatment of chordee in hypospadias. This operation should be done when the child is 2½ years old. A ventral incision is made and the fibrous corpus spongiosum is dissected out. With the penis bent back over the hand, lateral hindering bands are also dissected out. Scissors are used to free the skin laterally and up under the foreskin where right angle cuts are made to lengthen the skin. It is usually necessary to make other lateral cuts near the scrotum or any other region in which lengthening is required, but at the finish the ventral surface must be smooth without any redundancy or lumpiness of the skin. The incision is carried entirely around a No. 14 Foley catheter which has been put into the urethra. As the fibrous tissue is dissected out, the urethra moves backward, but do not cut off the cuff of the urethra as it will not leave enough urethral mucosa to easily reach the surface when healing has taken place and stricture will occur. Only spurting vessels are ligated. The urethra is sutured about with interrupted 0-0-0 plain catgut. The subcutaneous tissue and skin are closed with 0-0-0 plain catgut. If tension is present, a dorsal incision may be made without suturing. One is usually necessary at the junction of the penis with the abdomen. I have not found it necessary to suture the penis up over the abdomen. The penis is dusted with sulfanilamide powder. A pad is put over it, and adhesive tape is fastened to the thighs and brought diagonally across and another piece directly up the midline, so that the penis is in this manner strapped up over the abdomen, but the strapping must not be tight. The child will require some sedation. A 2½ year old child can be kept reasonably comfortable with $\frac{1}{16}$ gr. of morphine every 4–6 hours and one, 1 gr. nembutal suppository at night which may be repeated. The catheter is connected with a bottle by a plastic tube. On the fourth day, the dressings are removed and the catheter is removed. There will then develop considerable edema of the penis which will subside within about three days and is of no consequence.

There are cases in which the penis is in marked ventral curvature, and in which from the region of the frenum to the urethra there is very little of the corpus spongiosum, but proximal to this, one will feel a dense fibrous corpus spongiosum running down to the region of the bulb. Just as the urethra lies below the corpus spongiosum in the ordinary case of hypospadias, so, too, in these cases, it lies below the fibrous bulb. This fibrous band must be dissected out just as if it were anterior to the urethra.

I do not believe that operations for transplanting the foreskin to the ventral surface of the penis are of value. In fact, I think they are a distinct drawback when it comes to building the urethra, nor do I believe that operations that have been devised for transplanting the foreskin to the dorsal surface of the penis are of value.

Diversion of the urinary stream is necessary for a successful urethroplasty. Culp has very successfully used a retention catheter, thus avoiding an external urethrotomy. I have previously described a method for doing external urethrotomy in hypospadias. This consists of passing a No. 16 Foley catheter through

the urethra into the bladder, and passing it in for a considerable distance so that the catheter is curled up in the bladder. Now, a straight stylet about 8 inches in length (I use a bone pin), is passed down through the catheter so that its tip within the catheter can be used to make the catheter prominent in the perineum. Having cut down upon the catheter, the stylet is used to lift the catheter into the wound, which is then grasped with a pair of forceps to keep the proximal end of the catheter from being pulled out of the bladder. The distal end is caught by a pair of forceps and pulled out through the perineal incision. To do this, it is advisable to cut off part of the funnel tip of the catheter. The object in using a straight stylet is that it is easily introduced and, what is more important, is easily removed (fig. 1).

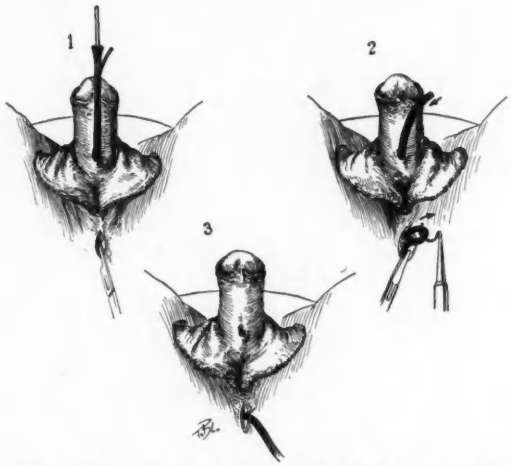

FIG. 1. Cecil operation for external urethrotomy drainage

The urethroplasty is best done between 4 and 5 years of age. Like tonsillectomy, children stand this operation better than older individuals. Erections do no damage to these children, but if one has to operate upon an individual beyond the age of puberty, erections are best combated by leaving nothing to chance, and every night for at least 5 or 6 nights, give HMC No. 2 or less quantity according to the age of the patient. I believe this is far more satisfactory and direct than depending upon estrogens or bromides.

There are four technical essentials for the construction of a urethra in hypospadias: 1) lack of tension; 2) a strip of undetached skin running from the hypospadias opening to the tip of the penis; 3) broad-bearing surfaces; 4) diversion of the urinary stream either by external urethrotomy or by retention catheter as advocated by Culp.

An operation which I have previously described and which has been used with uniformly good results by Cabot, Culp, Kimbrough and others, I believe most perfectly fulfills these requirements.

The operation which I devised is a modification of Bucknall's operation. The Bucknall operation had much in its favor, but there was one fault, namely, that in using the skin of the scrotum to form a part of the urethra, hair grew into the urethra and calculi formed on these hairs. It, therefore, occurred to me that it was not necessary to use any skin from the scrotum whatsoever, and so I devised an operation in which the urethra was formed from the skin of the penis and this was then buried in a midline incision in the scrotum. In cases of bifid scrotum or perineal hypospadias, a layer of deep scrotal tissue is inter-

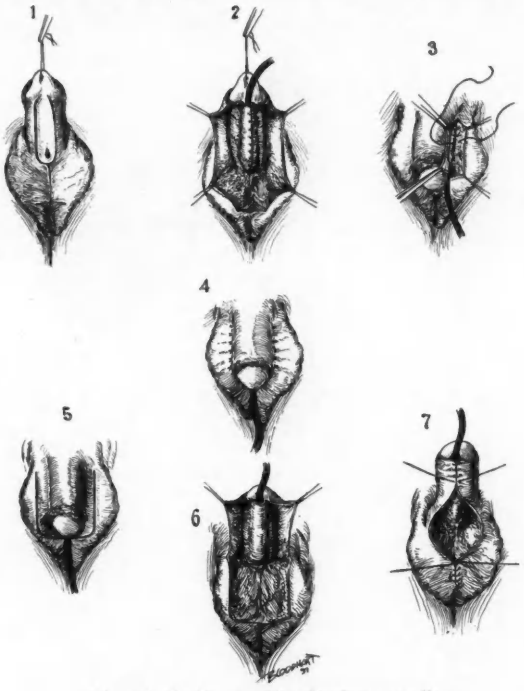

FIG. 2. Cecil operation for hypospadias

posed to cover the scrotal segment of the new channel. (Culp.) The steps of this operation are illustrated in figures 2, 3 and 4.

The sutures used for constructing the tube are 4-0 plain catgut, and this same material is used for fastening the penis to the subcutaneous scrotal tissues. The skin layer is closed with interrupted silk. At the conclusion of the operation sulfa powder is dusted on the wound and no dressing is applied.

Culp's report last year before the American Urological Association on the use of this operation is one of the most comprehensive reports that has ever been published on the cure of hypospadias. Among the cured cases reported by Culp were 5 patients who had had two or more failures in the construction of the

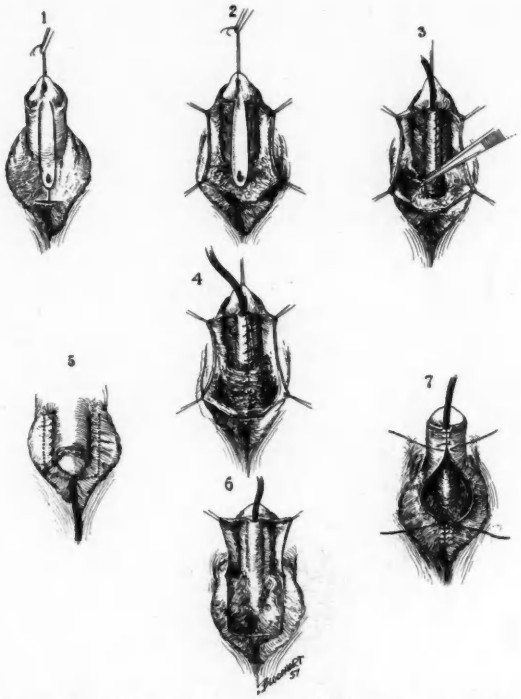

FIG. 3. Cecil operation to be used in cases of bifid scrotum or perineal hypospadias

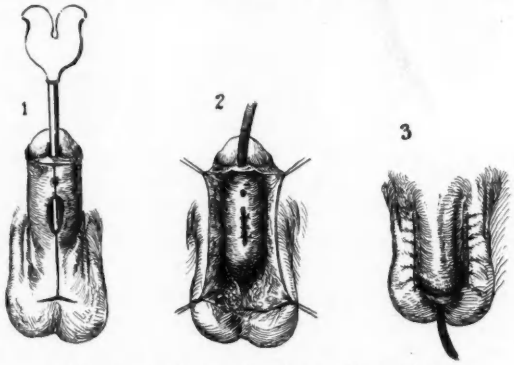

FIG. 4. Cecil operation for urethral fistulas

urethra, and 1 patient who was cured after 9 previous operations. The operation is not only one of the most satisfactory for the cure of hypospadias but as I have previously pointed out for the cure of urethral fistulas. It will undoubtedly play a large part in the treatment of war injuries of the urethra.

Denis Browne has recently revived an operation that was first described and illustrated by Duplay in 1880 and again in 1886, and was reviewed by me in 1936 in *Modern Urology* edited by Cabot. Duplay first originated the idea that a strip of skin left on the ventral surface of the penis, not made into a tube, would when enveloped by broad-bearing lateral flaps develop a urethral tube. He pointed out the value of broad-bearing surfaces in wide dissection of the lateral flaps. He used single sutures which were doubly locked, the single sutures not cutting holes as would loops, and sutured the skin edges with fine catgut. He described the dorsal relaxing incision. Duplay reported five cases that he had cured by this method. Burns has recently reported a series of cures in which he used the Denis Browne operation.

Any operation founded upon the four principles which I have stated will bring about the cure of hypospadias. It is my opinion that no operation will be so uniformly successful at all ages and in all cases, both in hypospadias and in the cure of urethral fistulas, as the technique which I have described.

Any operation that requires a child to be in the hospital more than 9 days, or that requires postoperative dilatation, or that results in fistulas, is not a modern operation for hypospadias.

1136 W. Sixth St., Los Angeles 17, Calif.

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EPISPADIAS: A REPORT OF FIFTEEN CASES

MEREDITH CAMPBELL

From the Department of Urology, New York University Post-Graduate Medical School, New York, N. Y.

Epispadias, known also as fissura urethrae superioris, in the male is characteristically a congenital defect in which the urethra opens on the dorsum of the penis. In the female the condition exists as a fission of the dorsal wall of the urethra and commonly extends to and involves the bladder outlet. Epispadias represents a lesser degree of the same embryologic developmental fault that produces vesical exstrophy and is always an anatomic component of exstrophy (figs. 1, 2, 3 and 4).

It is said that epispadias occurs about once in 30,000 individuals, and hypospadias is 150 times more common. Dees' statistical study of the incidence of epispadias suggests that it occurs, as deduced from hospital admission data (5,292,212) acquired by interrogation of several medical centers, about once in 117,604 males and once in 481,110 female admissions. It is notable that 15 or nearly a fourth of these recorded 56 hospital admitted cases of both sexes were at the Johns Hopkins Hospital where they were doubtless attracted by the skill and interest of Dr. Hugh Young who operated on 13 of them with reported good results in 12. Yet epispadias is probably not that rare. It was observed in three cases in 10,712 autopsies in boys studied by the writer, a ratio of 1:3570, as against 1:936 for bladder exstrophy. Fifteen personal cases have been seen, 12 of them in the office, and of this group which forms the basis of this communication, 13 have been operated upon. Epispadias associated with vesical exstrophy has been excluded from this study as has a most instructive sixteenth case in a 3-year-old boy seen in consultation with Dr. Edward Campbell of Philadelphia. More males than females have epispadias; the ratio in our 15 cases was 8:7. Being congenital, the condition has been observed at all ages, most of the reported cases being over 5 years of age; in our series two thirds were less than 5, and 3 were 8 years old (table 1).

This report is made largely to emphasize that when incontinence exists in epispadias, these patients should be surgically treated by plastic construction of a functioning bladder outlet and urethra rather than by ureterosigmoidostomy, the last method still being advised by some urologists and many general surgeons. By the plastic procedure not only can normal urination usually be established but the life expectancy of these unfortunate patients immeasurably extended over that so commonly observed to follow uretero-enteric transplantation.

ETIOLOGY

Among the many theories adduced to explain epispadias has been that of von Geldern (1924), the mechanical, which assumes rupture of the bladder during fetal life and consequent to obstruction which has subsequently disappeared. Keith's theory (1908) assumes the occurrence of intra-uterine ulceration of the

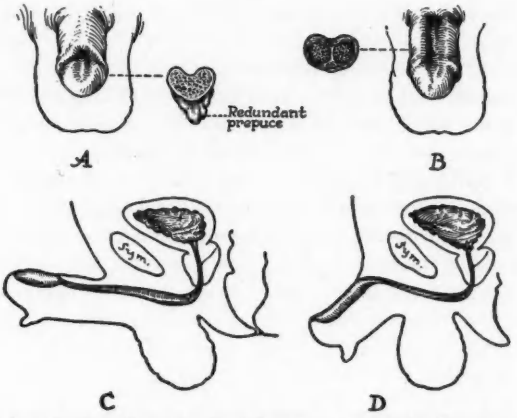

FIG. 1. Varieties of epispadias. *A*, glandular, rarest variety. Prepuce appears as a ventral hood. *A'*, lateral view showing slight dorsal chordee; urethra is continuous through superior segment of penis and terminates as a groove in glans (*C*). *B*, penile; meatus opens at base of the organ, corpora cavernosa being partially divided. Note absence of corpus spongiosum. *D*, schema of condition in B; proximal urethra is normal.

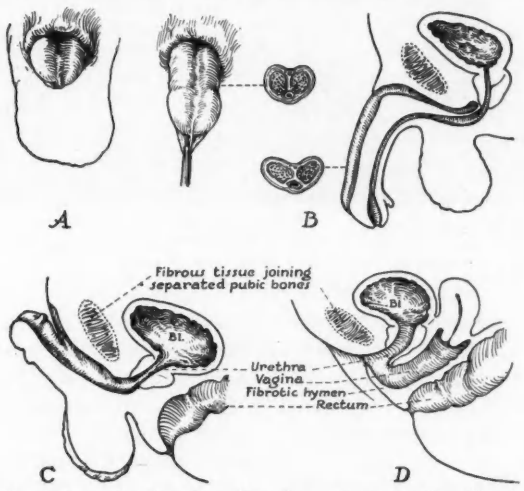

FIG. 2. *A*, subsymphyseal epispadias. *B*, subsymphyseal epispadias in case 2, table 1, canal being essentially a reduplicated or accessory urethra ending blindly in a slight bulbous dilatation at triangular ligament. Excision. *C*, complete epispadias in male representing a first degree exstrophy. *D*, complete epispadias in a 13 month old girl (case 2) in which bladder was widely opened to outside, there being no true urethra. Vagina was obstructed by an extremely dense, fibrotic imperforate hymen and cervix was lobulated but could not be proved to be reduplicated. Congenital solitary right kidney coexisted.

anterior bladder wall of the fetus. Mall (1908) and Wyburn (1937) attribute the anomaly to failure of mesoderm to develop locally and Gillies hypothecates a forward displacement of the cloacal membrane with failure to develop of the

mesodermal structures comprising the abdominal wall from the genital papilla to the umbilicus.

The hypothesis of Patten as reported by him at the 1950 meeting of the American College of Surgeons and based on embryological studies by him and his associates seems the most logical. Patten et al. rather reverse the usual explanatory sequence and believe the key to exstrophy lies in the embryology of epispadias. Granting that opportunities to study the embryologic development of epispadias in the human are wanting, they postulate a series of hypothetical stages in disturbed development which seem to explain the manner in which these associated anomalies may arise. They begin with the paired condition of the primordia of the genital tubercle which, as predisposing to epispadias and exstrophy formation, appear a little too far caudally with reference to the bladder outlet. This displacement would cause the primordia to lie at the level where the urorectal fold divides the original cloacal orifice into urogenital and

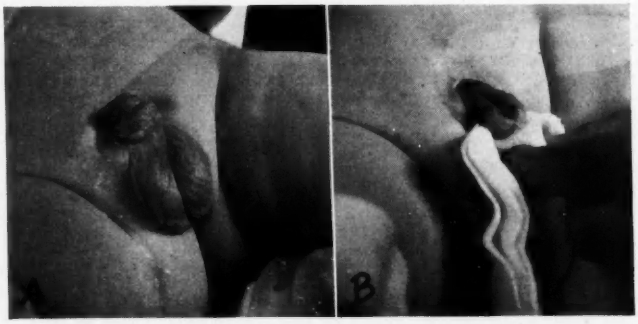

FIG. 3. Complete epispadias in a 14 month old boy. *A*, appearance showing stubby, stapulous penis with normal scrotum and descended testes. *B*, penis drawn forward showing divided corpora cavernosa and funnel-like extension of urethra beneath symphyseal band into bladder. Note pronounced ventral preputial redundancy.

anal outlets. Under such circumstances the corpora cavernosa would be formed just caudal to the urogenital outlet and the urethral groove would develop in their dorsal rather than in their ventral angle as is normally the case. Failure of midline conversion of the displaced paired primordia would account for the not uncommon exaggeration of the associated anomalies in which the penis or clitoris is represented by separate halves and molded about a single corpus cavernosum.

The exstrophy so generally accompanying the epispadiac condition involves a failure to reinforce the ventral body wall by convergent ingrowth of mesoderm. Normally this mesoderm ingrowth first occurs just cephalic to the urogenital orifice when the paired primordia of the genital tubercle meet each other in the midline. If these paired primordia are caudally displaced, this crucial spot remains over long without mesodermal reinforcement. Under these circumstances, when the urogenital membrane ruptures, the opening into the presumptive bladder region will be much larger than normal and tend to extend in the midline

to the umbilicus. The likelihood of such an extension is enhanced by the exceedingly rapid elongation of the region between the urogenital orifice and the umbilical cord which occurs at this stage of development. Even slight retardation of mesodermal ingrowth under such circumstances would in all probability mean a delay in reinforcing the region sufficient to account for the characteristic extensiveness of the exstrophic defect. Thus is explained not only the genesis of the minor epispadiac developments but also those involving lack of development of the urethra and the bladder outlet—the type so commonly seen in the female as it was in the seven young girls in our series.

CLINICAL MANIFESTATIONS

All gradations of epispadias occur, the incidence of the condition being in direct ratio to its gravity (fig. 1). Of the incomplete varieties in the male, the simplest yet the rarest is the glandular or balanitic in which the urethral opening is above and behind the glans (fig. 2). The dorsal groove indents the glans forward to its tip and causes this portion to be flattened out.

In penile epispadias the urethral opening may be at any point from the postglandular sulcus to the suspensory ligament and is generally near the base of the penis (fig. 1, *B*). The dorsum of the penis is therefore grooved from the epispadiac meatus to the tip of the glans or may terminate proximally. In one of our cases (No. 12), the epispadiac canal was that of a reduplicated or accessory urethra extending back to the triangular ligament (fig. 1, *C*). The sulcus in epispadias is covered by urethral mucosa and is frequently dotted with the orifices of the ducts of the peri-urethral glands. The prepuce hangs ventrally as a loose tag (the reverse of hypospadias) and leaves the broad flattened glans uncovered (fig. 3). The corpora cavernosa are usually widely separated and the corpus spongiosum is hypoplastic or may even be absent. As a rule the organ is smaller than normal, is spatulous in appearance, and incurved upward. Prostatic development is poor, is often incomplete above or is here entirely lacking. Because of these defects and even though erection occurs, intercourse is difficult or impossible and in the more severe forms of epispadias insemination will not occur.

In penopubic or subsymphyseal epispadias the urethral defect extends beneath the pubis to or nearly to the triangular ligament; when the defect does not involve the triangular ligament and the external sphincter muscle, urinary control is generally normal as it was in five of our cases in the male.

In complete epispadias in the male, the urethra is open to the bladder neck as a broad deep funnel and the condition is often associated with early degrees of vesical exstrophy (figs. 1, 3 and 4). In 6 such cases (females) in our series, the finger could be inserted into the open bladder outlet. The pubic bones are usually ununited and sometimes are rudimentary (fig. 4, *B*, *C* and *D*). Yet the separated bones are joined by a dense fibrous transpubic band. For these reasons complete epispadias may be considered a first degree of exstrophy, and with negligible or no sphincter development total incontinence is the rule. In case 3 the verumontanum was unusually large and in case 10 there was bilateral cryptorchism with a congenital hydrocele of the cord and hernia on the left side.

TABLE 1

CASE	SEX	AGE	INCONTINENCE		EPISPADIAS		PUBIS		GENITALIA		UPPER URIN. TRACT		CYSTOGRAM PREOP.	(CAPACITY) POSTOP.	OPERATION	RESULT (CONTROL)	TIME TO ACQUIRE NORMAL CONTROL	ADDENDA
			Since birth	None	Complete	Incomplete	Separated	Normal	Excoriated	Divided clitoris	Kidney	Ureter						
1. J. L.	F	3 yr.	+		+		+		+	+	Normal	Normal	Small	Normal	Young, complete[1]	Excellent	3 mo.	Normal 20 years postoperative
2. C. B.	F	3½ yr.	+		+		+		+		Cong. absence left	Absent left; strict. right	Small	Normal	Young, subpubic repair[2]	Excellent	18 mo.	Absent left kidney and adrenal confirmed by exploration.
3. E. T.	M	14 mo.	+		+		+		+		Normal	Normal	Small	Normal	Young[3]			Died postoperative
4. E. G.	M	8 yr.	+		+		+		+		Normal	Normal	Small	Normal	Young[1]; late closure of postoperative fistula	Excellent	1 yr.	Normal; now in college
5. D. D.	F	3 yr.	+		+		+		+	+	Normal	Normal	Small	Normal	Young[1]	Excellent	2 yr.	Behavior problem; masturbation, encopresis.
6. G. C.	F	2½ yr.	+		+		+		+	+	Normal	Normal	Small	Normal	Young[1]	Fair	2 yr.	Behavior problem; encopresis. Bladder capacity 7 ounces.
7. G. S.	F	3 yr.	+		+		+		+	+	Normal	Normal	Small	Normal	Young[1]	Excellent	1 yr.	Does semiprofessional dancing.
[8. J. W.	F	8 yr.	+		+		+		+	+	Normal	Normal	Small	Normal Lt. uret. reflux	Young[1]	Excellent	1 yr.	Normal development
9. D. L.	M	21 mo.	+		+		+		+		Normal	Normal	Small	Smaller than normal	Young[3] on bladder neck and deep urethra. Thiersch on penis (broke down).	Fair	2 yr.	Normal night and partial day control; steadily improving.
10. C. B.	M	32 mo.		+		Penopubic		+			Normal	Normal	Small	Normal	Ombredanne with scrotal hooding.			Poor cosmetic but good functional result.

11. J. B.	M	8 yr.		+		Urethra open to triang. ligament		+			Normal	Normal	Small	Normal	Ombredanne with scrotal hooding.			Poor cosmetic but good functional result.
12. J. O.	M	33 mo.		+		Penopubic Part of redup. urethra		+			Normal	Normal		Normal	Excision of subpubic epispadiac sac; closure of dorsal defect, patient having another urethra.			Moderate postoperative infection, but good end result.
13. D. H.	M	8 yr.	Occas.			Penile		+			Normal	Normal	Small		Browne[4]			Good result except for infection and separation of glandular urethra; to have secondary closure.
14. A. L.	M	4 yr.	+		+		+		+		Normal	Normal	Small		Refused			Operation refused.
15. T. S.	F	3 yr.	+		+		+		+	+	?	?			Refused			Operation refused.

[1] Young's complete operation for epispadias in the female.
[2] Young's subpubic correction of epispadias.
[3] Young's operation for epispadias in the male.
[4] Denis Browne's procedure for hypospadias applied to correction of epispadias.

In the female epispadias is generally of the complete variety; other types of lesser severity are designated as clitoric and subsymphyseal. The degree of bifid clitoris and prepuce and the wide separation of the labia and pubic bones reflect the severity of the malformation (fig. 4). The vagina and pelvic organs are usually normal. Yet in case 2 the imperforate hymen was a dense wall of fibrous tissue and the cervix was lobulated, and in case 7 the labia minora were notably absent as they so frequently are in epispadias in this sex.

As in all types of genital anomalies, the upper urinary tract is maldeveloped in about one in three cases. In case 2, there was left hemi-atrophy of the trigone

FIG. 4. Complete epispadias. *A*, in a 3 year old girl. Cleft clitoris with pronounced vulvar and peri-anal excoriation consequent to continuous urinary leakage. *B*, schema of conditions present. *C* and *D*, complete epispadias. Cystography in patient shown in *A* and *B*. *C*, note absence of symphysis. Catheter is coiled in bladder which would retain no cystographic medium. *D*, postoperative cystogram; essentially normal capacity, normal urinary control.

with congenital absence of the ureter and kidney above, while in a sixteenth case not included here, nephrectomy for congenital infected right hydronephrosis had been performed at 6 weeks of age.

There is often incontinence which unfortunately sometimes causes the child to be treated for enuresis; excoriation of the skin by the continuous wetness may be extremely painful and the child is usually marked for social ostracism (fig. 4, *A* and *B*). Urinary incontinence and its sequels together with the malformation itself are the clinical manifestations and as these children with epispadias grow older, they or their associates note the abnormality which, though asymptomatic, may produce a marked genital fixation complex (cf. Novak, 1948). In rare instances there may be stenosis of the external meatus of the epispadiac canal.

DIAGNOSIS

This is made by inspection in which the anatomic conditions previously described will be observed. Often the finger can be introduced through the epispadiac canal directly into the bladder. Excretory urographic study is advised in these cases as there is approximately a one-in-three chance that the upper urinary tract is also anomalous; moreover, other unsuspected disease of vital importance may be disclosed.

TREATMENT

This is surgical and properly executed according to indication may be expected to restore the penile urethra to a normally functioning canal which discharges at the usual site or, when the patient is incontinent, to construct a vesical outlet which, aided by subsequent surgical stricturization, will instate normal bladder function and schedule of urination.

In the construction of a new vesical outlet, the operation should be postponed until the child is at least thirty months of age—in short, until the age at which vesical control is normally achieved. Even after this age, the patient is certain to have some difficulty in learning to void and control his bladder, for it is a new and important experience which has previously been denied.

Young's operation with modification has given the best results in our hands in the correction of the incontinence in epispadias (figs. 7 and 8). In 8 of the 9 cases in which we have employed this procedure (5 females; 3 males), the incision has been through the midline dividing the pubes and widely exposing the vesical outlet and entire urethra. In case 2, a 3½-year-old girl, the procedure was carried out from below and with a most satisfactory result. As shown in figure 7, the urethral mucosa at the vesical outlet and in the adjacent urethral segment is largely cut away, leaving only a narrow strip, usually not over 3 to 5 mm. wide, but attempting to leave as much as possible of the musculature at and adjacent to the vesical outlet. This large muscle mass is then sewn together with No. 0 chromic gut, closing over both the urethral strip of mucosa remaining on the urethral floor and a fine (30) stainless steel suture wire which passes from above through the open bladder, the bladder neck, the urethra, and out the meatus for future use as a guide for a tunneled sound should this become necessary for urethral dilation three weeks or so postoperative. Fortunately we have had to use this guide in this manner in only one case (No. 6). Young reported a dense postoperative fibrotic occlusion of the bladder neck following the operation in one of his cases.

Following division of the pubis for direct access to the bladder outlet, and its closure with silver or stainless steel wire, no cosmetic or orthopedic difficulties have been observed in the children reported here (figs. 4, *A* and *B*, 5, and 6). That this procedure is unlikely to cause physical disturbances or handicap is suggested by case 7, a girl now seven years old who, two and a half years postoperative, engages without discomfort in semiprofessional acrobatic dancing (fig. 5).

When the operation is performed with splitting of the pubes, urinary counterdrainage is established by cystostomy tube (fig. 8). In the correction of penile

epispadias, perineal urethrostomy drainage is satisfactory as long as perfect tube function can be maintained. In two of our cases the perineal tube (16F balloon catheter) ceased to operate properly because of phosphatic and mucus deposit;

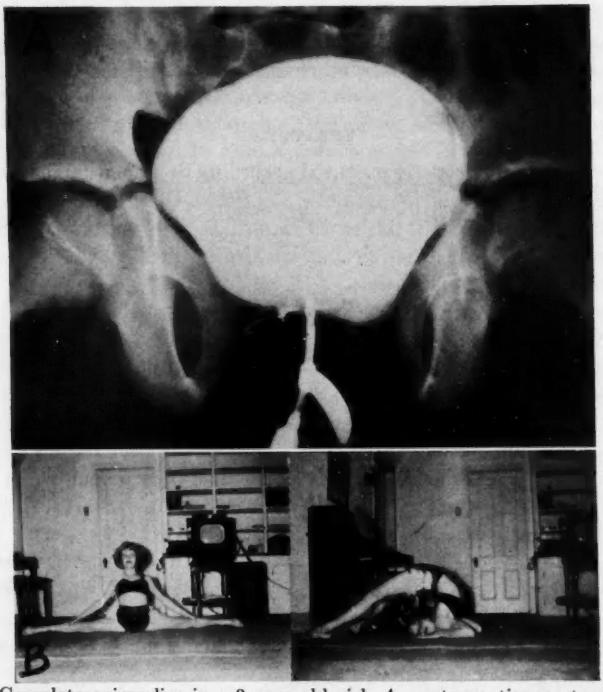

FIG. 5. Complete epispadias in a 3 year old girl. *A*, postoperative cystogram showing relatively normal bladder outline with normal capacity, absence of symphysis and silver wire with which symphyseal pubic band was sutured together. Normal control. *B*, *C*, 2 years postoperative; patient engaged in acrobatic dancing; no orthopedic difficulties nor physical handicap.

FIG. 6. Complete epispadias in an 8 year old boy. *A*, dorsal penile fistula developing postoperative, and requiring secondary closure with perineal urethrostomy counterdrainage. *B*, late result following closure of fistula in *B*. (Sound in urethra.)

some urine passed forward in the urethra to incite local wound breakdown in one instance but which spontaneously closed with the re-establishment of proper drainage.

Plastic construction of a penile urethra can be performed by any of several

methods; the writer has employed that advocated by Young (fig. 8) in three cases, the Thiersch technique in one case, and has used the Denis Browne pro-

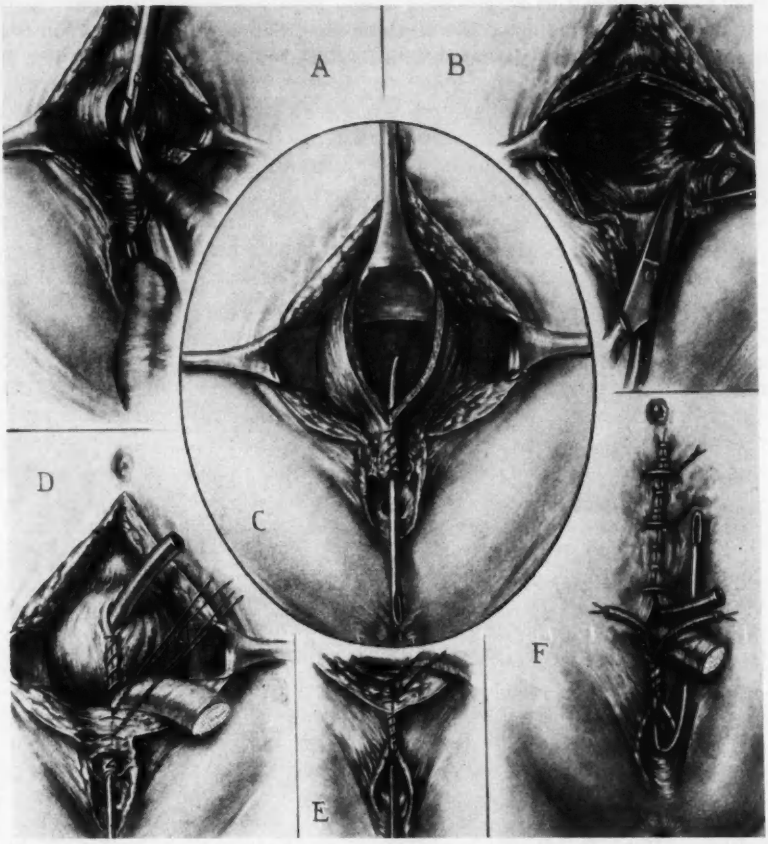

FIG. 7. Young's operation for complete epispadias in female. *A*, laying open of bladder outlet and entire urethra by division of pubis. *B*, excision of mucosal redundancy at bladder outlet; our practice is to excise mucosa considerably more widely than Young indicated but to leave a mass of muscle tissue as large as possible about the bladder outlet. *C*, closure of bladder outlet and construction of urethra about a small silver probe as recommended by Young. Author prefers to use a steel wire for this in order to get closure of maximal tightness and to leave wire in situ as a guide for passage of a tunneled sound 2 to 3 weeks postoperative should this become necessary as occurred in one of our cases. *D*, closure of bladder about a suprapubic drainage tube. A cigaret drain is left in the space of Retzius for 48 to 96 hours. Approximation of interpubic fibrous band using silver or steel wire. *E*, *F*, external closure. (Redrawn after Young.)

cedure in 2 cases. The Browne procedure is carried out substantially as it is employed in the correction of hypospadias.

In two cases without incontinence (Nos. 11, 12) a modification of the Ombrédanne operation for hypospadias was employed to construct the subpubic and

adjacent urethra, the shiny hairless mucosa-like skin being mobilized from the subpubic and prepubic areas in pouch formation and reflected forward. Dorsal penile skin mobilized as longitudinal lateral flaps which were brought together in tube formation, completed the urethral construction proper. After constructing the new penile tube, the penis with its dorsal raw areas was implanted in a

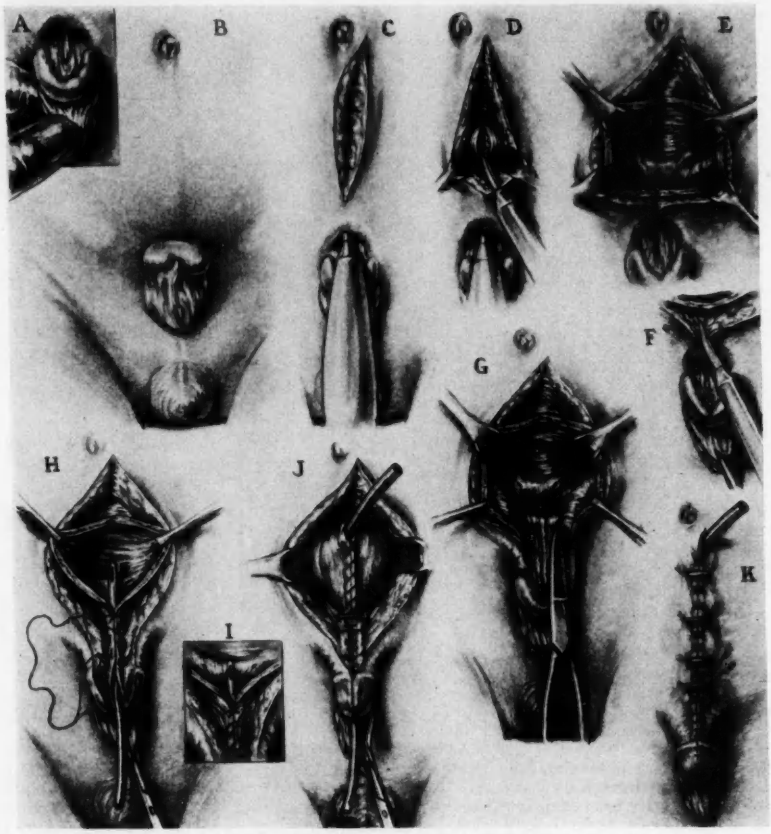

FIG. 8. Young's operation for correction of complete epispadias with incontinence in male, various steps being essentially those given in legend of figure 7 but here, in addition, showing plastic correction of epispadias. (Redrawn after Young.)

tunnel made beneath the skin of the anterior scrotum and, when healing occurred, the penis was liberated much as in the Cantwell operation for hypospadias.

Having performed the operation to establish urinary continence in epispadias, the surgeon should not feel that he has failed if the patient leaks immediately postoperative. In two of the writer's cases the achievement of perfect control took as long as 2 years (table 1). Here grave behavior problems retarded normal bladder control despite a technically satisfactory operation; in one girl the mis-

behavior included masturbation, tantrums, and habitual and intentional encopresis (defecating in bed). In another girl equally problematic, bladder control was bought by rewards.

In older cooperative children control is usually acquired much earlier than in the young; its acquisition may further be stimulated postoperatively by practice of the start and stop urinary exercises wherein the patient, as he voids, stops the stream and starts, again stops and starts, until he has emptied his bladder. Thus the patient learns to exercise new sphincter control and becomes conscious of the desire to urinate and of the associated mechanics of bladder emptying. In these cases perfect control is rarely achieved until the cooperative patient becomes fully conscious of what is expected of him. While most of these patients show nearly normal control immediately or soon after operation, we do not consider them cured until they have perfect control, both day and night and the urine is sterile.

When a satisfactory sphincter cannot be reconstructed, and this merits at least two trials, and if the rectal control is normal, ureterosigmoidostomy must be considered but to be employed only as a last resort. Thirteen of the author's fifteen cases were operated upon with satisfactory results with the exception of one operated upon at twenty-one months of age and who can hold his urine all night but leaks when up and about; reoperation will probably be necessary. One child, a boy of 14 months, died postoperative; today's improved supportive care would have saved him (fig. 3).

In one instance of penile epispadias treated by the Browne method the penile canal healed soundly but the urethral segment of the glans reopened, and will require subsequent closure. In another boy operated upon by Young's method (case 4), a dorsal urethral fistula required secondary closure (fig. 6).

SUMMARY

The salient features as observed in 15 personal cases of epispadias are discussed. When incontinence exists, adequate attempts should be made by plastic surgery to instate normal bladder control before ureterosigmoidostomy is seriously considered. In the 11 cases with complete urinary incontinence here reported, normal control and bladder function were achieved in 7 with good nocturnal but partial diurnal control in 1, one died postoperative, and in 2 operation was refused.

140 E. 54 St., New York, N. Y.

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DISCUSSION

Dr. George Gilbert Smith (Brookline, Mass.): There are some questions I would like to ask Dr. Edgar Burns. Do you free the lateral edges of the strip of skin at all?

Do you suture the skin on the dorsum of the penis after making the longitudinal slit?

I should like to ask Dr. Campbell a question, also. When you expose the bladder neck and the urethra through the suprapubic approach, what muscle do you find to bring together around the urethra to give control? Can you identify the external sphincter at that time, or what muscle do you get?

Dr. Richard Chute (Boston, Mass.): Specifically, I should like to ask Dr. Burns when, after the final stage, he discontinues the perineal diversion of the urinary stream.

Dr. John K. Ormond (Birmingham, Mich.): I should like to ask Dr. Campbell a question about the repair of the split symphysis there. Do you merely, after splitting it, leave it as it was, or do you make effort to bring it together? Does that have any effect, at all, on the sacro-iliac joints or the sphincter?

Dr. Ormond S. Culp (Rochester, Minn.): Dr. Cecil has asked me to comment on his paper inasmuch as I have performed the Cecil operation on thirty-one patients.

The chance of having universal agreement on the choice of operation for the repair of hypospadias is as remote as complete unanimity of opinion regarding the best type of prostatectomy. I could be content with several types of urethroplasties except for their common implications.

My first and last patients repaired by the Cecil method have had comparable results. There have been no fistulas or other undesirable complications. In one case diversion of the urine was omitted and the patient used his new urethra immediately. The suture line leaked for awhile, but within two weeks all urine was passing freely from the new meatus. Burying the newly constructed urethra in the scrotum appears to be safe and dependable prophylaxis against fistulas, which have been the nemesis of most other operations.

Does this operation have any intrinsic disadvantage which might detract from its cardinal virtues? Some surgeons may object to the fact that it requires two stages for construction of the new urethra. I have derived no end of comfort and satisfaction from the knowledge that only two operations will consistently produce excellent results without fistulas.

(Slide) This is a summary of five patients who had from two to nine previous operations for construction of the urethra with complete failure. All were cured by the Cecil operation. All would have done well to have settled for two operations in the beginning.

Some urologists may object to the fact that the newly constructed meatus is not at the tip of the glans. A meatus in the region of the frenum (as shown in this slide) is quite serviceable (as demonstrated by these urinary streams).

(Slide) Age of the individual is of no consequence. Most of our patients were corrected before they started to school. Here is a typical result with a child five years of age. The operation works equally well on adults.

(Slide) Here is a young adult who had nine previous operative failures. He was first able to urinate standing up when he was a senior in college.

(Slide) Although most of our patients had penoscrotal hypospadias, this case shows successful construction of new urethra from the perineum. The Cecil operation conserves so much penile skin that some of our patients may have to be circumcised later. This might be considered a disadvantage, but it certainly is not a serious one.

(Slide) There is only one pitfall in the operation. One must be careful when constructing the urethra at its termination to avoid undue tension that might produce sloughing and displacement of the new meatus posteriorly.

Surgeons who have perfected their preferred operative technique so they have no fistulas or other complications may forget what I have said. Those who do only an occasional case or those who are still plagued by the common undesirable postoperative sequelae would do well to try what we think is probably the most foolproof method for curing hypospadias.

Dr. John K. Ormond (Birmingham, Mich.): I had occasion to observe twenty-four of Dr. Culp's patients, and I agree with everything he has to say.

Dr. Reed Nesbit (Ann Arbor, Mich.): This symposium cannot be complete unless one mentions the work of Dr. Wehrbein who, as a guest of this society, read an important paper upon an operation of his own design which, after all, is a modification of the Cecil operation. It has certain advantages over Dr. Cecil's technique. It appeared in the *Journal of Urology* (vol. 50, pp. 335–340, 1943). I suggest that you all read it.

Dr. Edgar Burns (Closing): First, I should like to answer Dr. Smith's question. The lateral edges of the skin strip are not raised. They are not disturbed at all. The defect created by the dorsal slit is not sutured, and epithelium covers the area in an amazingly short period of time, usually within the first two or three weeks.

Dr. Chute asked at what period the perineal urethrostomy tube is removed. This is usually done about the tenth or twelfth day, when the wound appears to be healed. The sutures are removed the same time. The patient may leak some urine through the perineal opening during the first 24 to 48 hours, but we have had no cases that leaked after that time. Some of them didn't leak at all.

Someone has asked a question regarding fistulas. Out of seven cases, we have had one fistula, which occurred at the penoscrotal juncture, and that was my fault. I repaired the urethra too soon after the straightening operation was done, and the circulation in that area had not had time to fully develop, a point that was emphasized in the body of the paper. I believe that at least a year should elapse between the straightening operation and the final repair.

Dr. Meredith Campbell (Closing): Formerly we used silver wire for the closure of the dense interpubic fibrous band which extends between the two bony stumps; now we use steel wire.

The musculature around the bladder outlet is usually adequate for plastic repair. There is no urethra; in females the "urethral" orifice is just a hole in the side of the bladder. By mobilizing the vesical outlet, a large mass of muscle is made available to build up a good "sphincter" and with this tissue is also constructed, even in small females, a urethra.

There is one trick in the Denis Browne operation which you may find helpful. With edema, a plastic bead digs down into the skin and may pull through. I use an ordinary pearl button one quarter of an inch in diameter and this gives a little more spread of the suture tension. There should be no pull, but with edema there may be. In our hands the buttons have worked much better than the plastic beads.

THE EVALUATION OF HORMONAL THERAPY IN CRYPTORCHIDISM

CLYDE L. DEMING

From the Department of Surgery, Section on Urology, Yale University School of Medicine, and the Grace-New Haven Community Hospital, New Haven, Conn.

After 25 years of prescribing and using hormones for the treatment of cryptorchidism, it is time that we arrive at some definite evaluation of the therapy. Hasty and incomplete clinical observations, coupled with too little regard for research, have given the pediatrician who first views these patients a misconception of the actual facts. Webster claimed that the use of hormone caused 90 per cent of cryptorchids to migrate to the scrotum, while Lowsley claims zero per cent. The literature contains many reports of percentages between these two extremes. The age at which hormonal therapy should be given has also been a point of contention. Some advise its administration from the second year on through puberty; others support hormonal therapy in full-grown adults. The type of hormone used, the length of time of its administration, and the amount given vary in different clinics. The preceding points of contention should now be clarified and a regime of treatment be determined which is rational and will give constant results in the hands of all physicians.

There is no doubt that the chorionic hormone, the so-called anterior pituitary-like substance derived from pregnancy urine, is a factor in the mobility of the undescended testis. The experimental work of Engle, Moore, DeJongh, Bourg, Deming and others conclusively demonstrates this contention. Womack and Koch found the greatest amount of this hormone in the foetus, that it was practically absent in boys up to 10 years of age and that it was present in large amounts during adolescence and up to 40 years of age, after which it gradually declined in amount. The testis usually descends into the scrotum between the seventh and ninth month *in utero*. It is estimated that 1 per cent of the testes is undescended at birth. There is no doubt that some descend at puberty. After the adolescent period is past one would not expect the cryptorchid to descend and this has been our clinical experience. The biological and clinical pictures support the action of this hormone.

Before birth and at birth, under normal conditions, both testes have an equal opportunity to descend into the scrotum. Clinically, unilateral cryptorchids far exceed the bilateral lesion. If one testis descends and one remains a cryptorchid there must be some factor other than hormonal which influences the retention of the testis along the canal, such as abnormal attachment of the gubernaculum, deformity of the organ, hernia, hydrocele, ectopia, or malformation. There may be a congenital absence of the organ. If both testes remain cryptorchids then one might hypothecate that, with normal gonads and in the absence of obstruction, there may have been *in utero* a subnormal amount of the hormone present at the opportune time for descent. Assuming this condition, an ideal situation would be present for a successful descent after hormonal therapy.

The motive force which causes a descent of the testes is not present within the

testis, nor is the gubernaculum responsible for its descent, for the latter only guides the direction of movement. Thompson and Heckel and Moore and Tapper have referred to the absence or near absence of the cremaster muscle in the cryptorchid. Hart has clearly shown in his experimental work on the marsupials that the cremaster muscle exerts a milking action on the testes and that the gubernaculum acts only as a guide. Further evidence is demonstrated in the author's work on the rhesus monkey. This animal is born with descended testes which, after four or five days, ascend into the abdomen or to the internal inguinal ring until adolescence, the sixth year, when they naturally descend into the scrotum.

The author's experimental work embraces a histological study and comparison of tissues before and after injection of gonadotropic hormone in pre-adolescent macaque monkeys. A section of the inguinal canal and cord were taken on one side as a control; and when, after a month's hormonal treatment, the remaining testicle had descended into the scrotum it was removed for microscopic study. The descended testes showed grossly a 50 per cent increase in size with histological evidence of an increase in the diameter of the tubules and some increase in interstitial tissue. The tubules of the epididymis had become larger at the expense of the intertubular tissue. The epithelial cells lining the tubules were taller and appeared more active but there was no gametogenetic activity. The vas had enlarged two or three times and had become elongated and the vascularity of the whole cord was greatly accentuated. There was an increase in the size of the lymph spaces with a deposit of fatty tissue, and the cremaster muscle fibers were twice the size of the control. Examination of the scrotum showed the dartos muscle to be greatly increased in size with large lymph spaces and increased vascularity but there was no change in the skin. The effect of the gonadotropic factor is not only to widen the inguinal canal but also to increase the size of all the cord structures and the scrotum except the skin and to cause the testes to descend into the scrotum without the development of hernia. The same conditions can be produced by hormonal therapy in the human male child as have been produced in the pre-adolescent monkey unless mechanical obstructive factors or structural abnormalities are present. These artificially produced tissue changes are comparable to those normally seen in the adolescent child, when the gonadotropic hormone is present in the greatest amount. If we can apply hormonal therapy in the child to cause the cryptorchids to descend into the scrotum without the development of sexual maturity we will have accomplished the desired result.

AGE

The testis must lie in the scrotum to develop to its fullest physiological extent, and it should occupy this position a number of years before adolescence. It would seem that it should be transferred before the seventh year, although we have no objection to earlier transference. We select any time between the fifth and seventh years at an age when the child can give assistance and before he realizes the abnormality and before he develops any inferiority complex. We should not wait until puberty before transplanting the testis into its natural location when nature

intended its transplantation fourteen years earlier. We have been unsuccessful in treating adults by hormonal means alone.

CASES FOR HORMONAL TREATMENT

It is quite obvious that not all cases of cryptorchidism are suitable for hormonal treatment. Contra-indications for hormonal therapy are found in boys with an ectopic testis or an accompanying large hydrocele or hernia. The most favorable conditions exist when the testis lies in the inguinal canal and cannot be forced into the scrotum or when there is a bilateral cryptorchidism whether or not the testes can be palpated. There is always a reason why testes do not descend into the scrotum. If both testes remain as cryptorchids one can hypothecate that the reason for failure to descend was a subnormal amount of the hormone at the eighth and ninth month *in utero* and can expect that these cases will respond to hormone therapy. One should rarely expect to be successful in the hormonal treatment of unilateral cryptorchidism because both testes have been subject to equal effects of the hormone *in utero*. The physician should exercise greater diligence in the examination of these conditions. One rarely sees a fully developed scrotum in a child with an intra-abdominal testis and the scrotum is never developed on the side where there is a congenital absence of the testis, so that there are, theoretically, only a few cases of cryptorchidism where a successful descent of the testes can be produced by hormonal therapy alone.

TYPE OF HORMONE

The hormone known as Follutin-S is the hormone used in our clinic. Usually 250 international units are given intramuscularly 3 times a week for 4 weeks for a total of 3,000 units. This amount is sufficient to produce an artificial adolescence with a slight edema of the foreskin and scrotum and the descent of the testis will follow in this period if it is to come down at adolescence. In other words, a false adolescence is produced. It will not cause much actual growth of the phallus or of pubic hair. The administration of lesser amounts over a longer period of time seems injudicious and the giving of more units unnecessary. Recently in the *Journal of the American Medical Association* the question was asked and answered as to hormonal therapy for the undescended testis. Advice was advanced that 30,000 units should be given over a six to eight week period in children 11 to 14 years of age. We can not subscribe to this advice. If too much hormone over too long a period is given there are adverse reactions which must be kept in mind, such as precocious sex development and closure of some of the epiphyseal bone centers, which prevents the full development of long bones. One must be fully cognizant of the harmful effects resulting from the use of the gonadotropic hormone as well as its value.

Androgenic hormone has been advocated by several authors as superior to the anterior pituitary-like hormone in producing a descent of the cryptorchid. In the male puppy, androgen causes an aspermia and loss of gametogenetic production. Heckel has reminded us of the diminished spermatogenesis in the human after male hormone therapy. If spermatogenesis is a factor to be desired androgen

should not be given for cases of cryptorchidism. We use androgen if the testes do not develop after they have been surgically transplanted to the scrotum.

It is quite evident that one can expect a full descent of the cryptorchids by the use of chorionic gonadotropic hormone alone in only a few cases, probably 5 per cent or less. Its greatest usefulness is as an adjunct to a surgical orchidopexy because it elongates all the cord structures, including the vas and vessels, and prepares the scrotum for reception of the testicle. A regular course of hormonal therapy is given preoperatively in selected cases and the surgical procedure done immediately. The technique of the operation is greatly facilitated and even in the most difficult cases sufficient cord length can be obtained by transplanting the testis beneath the deep epigastric vessels. We have never had to perform an orchidectomy after adequate preoperative hormonal therapy.

Of 189 cases of cryptorchidism, descent of the testis took place with hormonal therapy alone in ten cases, or 5 per cent. Of the 201 surgically treated undescended testes, agenesis of one testis was present in 9. Orchiectomy was required in 12 cases because of short vessels or a deformed organ, but only one of these patients had been subjected to preoperative hormonal therapy and that one inadequately. The main use of chorionic gonadotropic hormone is as an adjunct to surgery.

SUMMARY

The hormone containing chorionic anterior pituitary-like substance is of particular value in the treatment of cryptorchidism.

Follutin-S, 250 international units, given intramuscularly 3 times a week for a total of 3,000 units is sufficient.

Optimum age is the fifth year.

Hormonal therapy will cause the full descent of the cryptorchid in about 5 per cent of the cases.

Its greatest value is (as) an adjunct to surgery.

Surgical orchiectomy has never been necessary following adequate hormonal therapy.

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SURGICAL TREATMENT OF CRYPTORCHIDISM

JOSEPH H. KIEFER

From the University of Illinois College of Medicine, Division of Urology, Chicago, Ill.

The need for surgical correction of persistent cryptorchidism is now generally accepted. The failure of the retained testis to develop fully was described by John Hunter more than 150 years ago. The excellent and thorough work of Carl Moore proved the need of the testis for an environment at a temperature below that of the body normal.

While the failure to mature is the chief reason for bringing down the cryptorchid testis, there are others of importance. The possibility of malignant degeneration is of such magnitude as to demand consideration. Our own experience has been such that we feel that this factor alone warrants orchiopexy, even in the adult. The cosmetic factor, although not medically important, should not be disregarded.

Endocrine therapy of cryptorchidism has now assumed a different role from that assigned to it when it was introduced. It is now more often used as a test or as an adjunct to surgery rather than as a sole mode of treatment. We use endocrine injections before surgery in most prepubertal cases. This establishes whether or not the testis can descend into the scrotum with endocrine stimulation alone. If it can, and there is no separate indication for surgery such as associated hernia, the child is allowed to wait until puberty when the normal endocrine stimulus operating at that time can be expected to effect descent. If endocrine injections are ineffective, surgery is then done before puberty.

Most urologists make an effort to bring the testis down into the scrotum before pubertal changes begin to appear. There are some, a minority, who wait for a year or two after pubertal changes become apparent. We have felt that the testis has the best chance of responding to the endocrine stimuli of puberty if it is already in the scrotum at that time.

The surgical principles underlying the operation of orchiopexy are now well established. The desired result is to have the testis, with the spermatic vessels and the vas deferens intact, in the bottom or midportion of the scrotum.

The testis as well as its nutrient vessels and the vas deferens must be completely liberated. Fixation of the freed testis in the scrotum is considered necessary by most urologists today. It is relative to the method of fixation that most differences of opinion have arisen and different techniques devised.

The following is a brief description of the surgical technique we now use, with brief comments about alternative procedures that have been tried. Our technique is shown in figures 1, 2, 3, 4 and 5.

The usual inguinal incision is used, if necessary extended up beyond the anterior superior spine. The inguinal canal is opened and the testis, if there, is raised up. The gubernacular structures, if present, are dissected to their points of attachment and divided.

One must be careful in this original dissection not to injure the vas and epididy-

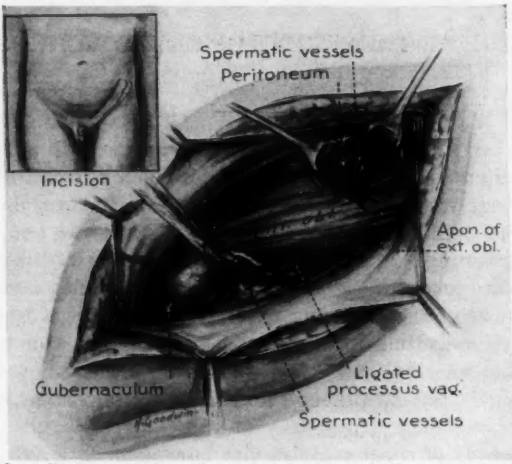

FIG. 1. Muscle splitting opening above inguinal canal. This is helpful in freeing spermatic vessels high in abdomen. Peritoneal cavity can also be opened and explored through this.

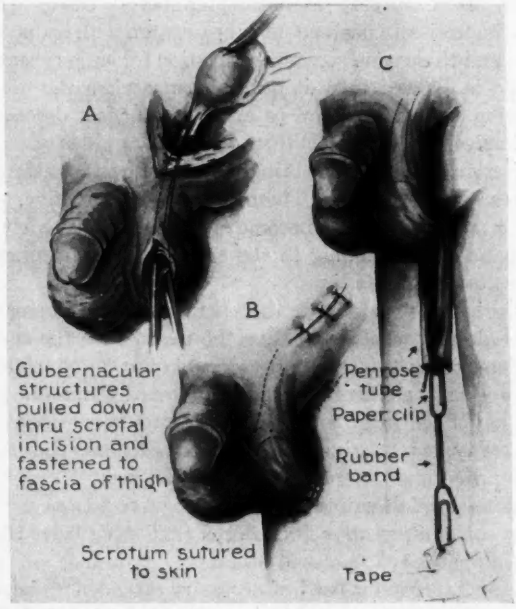

FIG. 2. Method of applying traction to testis after gubernacular structures have been attached to thigh.

mis. They are often not in normal relationship; commonly, the epididymis is separated from the testis except for the small area of the efferent ducts. In some

cases in which the testis is situated high in the inguinal canal or in the abdomen, the vas and epididymis may extend well down into the inguinal canal and then turn back to join the testis and this loop may easily be injured.

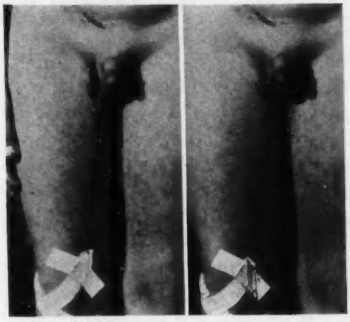

FIG. 3. After application of traction for many weeks

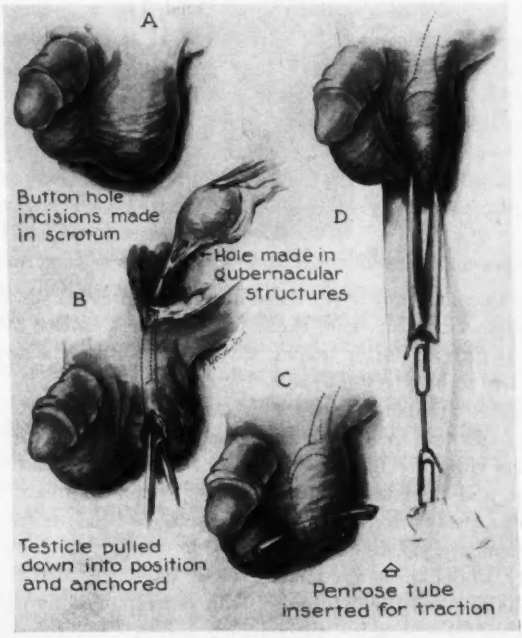

FIG. 4. Method of applying traction through a button hole made through gubernacular structures.

If the testis is not in the inguinal canal, abdominal pressure by the surgeon will often help to extrude it through the internal ring. If the testis is still not located, the processus vaginalis, if present, is opened and the finger inserted into

the peritoneal cavity. The testis may be felt in any direction, but commonly below or lateral to the internal ring. It is usually possible to bring it through the internal ring without great difficulty. If the testis is fixed up high in the abdomen, it is better to approach and free it intra-abdominally through a separate muscle splitting opening higher up.

One of the most important parts of the operation is the complete freeing of the cord structures from the overlying peritoneum of the processus vaginalis. The peritoneum is divided just proximal to the testis and removed completely. In cryptorchidism this peritoneum is much more adherent to the cord than it is in the ordinary inguinal hernia. The very tight adhesion between the peritoneum and the cord structures is an important factor in preventing complete descent. Injection of liquid by needle just under the peritoneum is a useful maneuver to develop the proper cleavage plane.

All connective tissue strands joining the peritoneum and the cord elements must be thoroughly and completely divided. Likewise, all remnants of the internal and external spermatic fascias as well as the cremaster muscle must be re-

FIG. 5. Button hole traction arrangement

moved. Failure to completely sever these fibers may prevent full descent or lead to later retraction. In most cases, these bands do not extend much above the internal inguinal ring and after freeing a very short ways inside the abdomen, the vessels are felt to be freely movable.

In an appreciable number of cases, however, this is not entirely true and one feels adhesions higher up inside the abdomen, even up as high as a full finger's length above the ring. We formerly followed the advice of Cabot and cut the internal oblique and transversus muscle fibers which comprise the conjoined tendon. This was always done with some reluctance because suture of the cut muscle ends is not always satisfactory.

More recently, under these circumstances, we have extended the skin incision upward, split the fibers of the external oblique correspondingly higher, and then made a muscle splitting opening through the internal oblique and transversus muscles about 4 or 5 cm. above the inguinal ring. By stretching this opening with the fingers and inserting retractors, one gets a very adequate opening into the extraperitoneal space. It is not necessary to cut the internal oblique and transversus muscles as recommended by Fruin and by Lewis. See figure 1.

The spermatic vessels are identified and exposed. A little tension on these

vessels helps to locate them. From this point they are freed completely from any peritoneal or other adhesions both down to the inguinal ring and up to a point above the pelvic brim, thus allowing the maximum extension.

If the testis cannot be located in the groin or near the internal ring, this type of incision allows one to do an intraperitoneal exploration. On removing the retractors, the muscles fall back to their normal positions immediately and one or two sutures are enough to make a sound closure. This maneuver is much more satisfactory than cutting the lateral fibers of the conjoined tendon. It gives exposure where needed and the closure is better.

Lack of length of the vas deferens is seldom a cause of trouble or of failure to bring the testis all the way down into the scrotum. As mentioned above, in many of these cases the epididymis is not attached to the testis and mere rotation of the testis allows sufficient extra length in the vas. In those cases where the vas is a little short, it was suggested by Frangenheim in 1920 that the testis and the spermatic vessels be brought underneath the epigastric vessels. This is done without difficulty but we have not found it to give much additional length, seldom more than 5 or 10 mm. It is not desirable to bring the cord structures under the epigastric vessels. If for any reason whatsoever, later surgery were done in this area, the exposed epigastric vessels might easily be injured and lead to troublesome hemorrhage. If they are in the way, it is much better to doubly ligate and sever the vessels rather than slip the testis underneath them and leave them intact in an abnormal location. We have not used the procedure of making a new artificial opening through the muscles medial to the epigastric vessels, as suggested by Fruin. By this method the cord emerges at about the same point as it does when the epigastric vessels are ligated.

The Ferguson type of inguinal canal repair is used because it brings the cord out through all the layers at the site of the external ring.

After the testis and its vessels have been completely freed from the surrounding structures and sufficient length obtained so that the testis may be brought well down in the scrotum, there is still the question of fixation. A few men have expressed the opinion that if the testis and cord have been adequately freed up, no fixation will be required. Those of this opinion are definitely in the minority. Most urologists believe that fixation is desirable. We have felt that fixation of one form or another is useful in practically every case.

The scrotum is nearly always small and underdeveloped and despite vigorous stretching to form a pouch there is a very strong tendency for the scrotal tissue to recontract, and force the testis back up to the neck of the scrotum or even to the external ring. It has been stated that complete sectioning of the cremasteric and other fascias and placing the testicle through the opening so made would prevent retraction. There will still remain the dartos fibers in the very skin itself whose action will tend to push the testis back up. Also, the cord structures will tend to contract and the scarring of the inguinal structures incident to healing can in itself cause retraction.

Methods of fixation advocated have been numerous and varied. The first recorded orchiopexy by Rosenmerkel in 1820 was described as including fixation

to the bottom of the scrotum with a suture. Suture of the testis to the bottom of the scrotum continued to be most popular, but apparently then, as now, proved to be inadequate. Procedures to fix the testicle in the scrotum by closure of the scrotal neck were next tried. Bevan's method was based on this idea. The procedure fell into disuse because of its ineffectiveness, particularly if there was still any tension on the cord structures. Other efforts to fix the testicle included transplantation both under the skin of the thigh or to the scrotal sac on the opposite side. Fixation by suture in other locations such as in the perineum or to the pubic bone was also tried.

When it was found that the retracting testis would pull the scrotum with it, the next step was to attempt to hold down both the scrotum and the attached testis. Sutures were placed through the bottom of the scrotum and through the skin of the thigh. Elastic or other materials were placed through the scrotum and attached to wire frames or to the adjacent or opposite thigh.

Suture traction was not completely effective because the tension could be maintained for only a limited period. Sutures cut through within a short time and as the tendency to retraction usually continued beyond this time, the method often failed.

The next step was to make a semi-permanent attachment of the testis to the thigh through skin incisions. Although Keetley first advocated this principle, Torek popularized it in this country, using sutures through the body of the testis itself. Torek's method had a serious disadvantage in that if wound infection occurred, the tunica of the testis might be so badly damaged that the parenchyma would be extruded and lost.

Keetley had advocated fixation to the thigh not of the testis itself but of the fascial structures attached to it. This obviated any damage to the testis by the sutures and simplified the later separation from the thigh. This method has since been redescribed by many authors. It is the method I was taught by Dr. Charles Morgan McKenna and I still use it in most cases. It provides excellent fixation, is easily detached, and I know of no serious objection to its use. More elaborate methods of fixation such as raising fascial strips or flaps have never become popular.

The methods enumerated so far were devised to fix the testicle in a certain place but not to move it further. It is true that elastic threads and attachments were used but they were attached to sutures which cut through the tissues within a short period, seldom over two weeks.

There are a few patients in whom continued traction is desirable. These are the ones in which most thorough freeing of the spermatic vessels still does not develop enough length to allow the testis to be brought well down into the scrotum but leave it high up in the scrotum or in the scrotal neck. Dr. McKenna would fasten the testis to the thigh with the thigh in the flexed position so that gradual straightening would tend to pull it down a little farther. The amount of additional length obtained this way was small.

There is no basic reason why it should not be possible to lengthen the structures of the spermatic cord by continued mild tension. This is true of practically all soft tissues elsewhere in the body. We have applied traction to the gubernacu-

lar structures after they have been attached to the deep fascia of the thigh. This has been tried in a small number of patients. It has been effective in some of them in loosening the tissue of the spermatic cord and bringing the testis down to lie more loosely and naturally in the scrotum. See figure 2.

The traction is easily applied using a small rubber tissue drain wrapped around the isthmus and connecting to a rubber band which in turn is stretched down to an adhesive plaster anchor on the inner side of the thigh just about the knee. The tension is easily adjusted either by changing the position of the anchor or by adding or subtracting small paper clips which are used as connecting links.

If the tension is applied mildly at first and gradually increased, most boys can wear this with no discomfort and no disability or restriction of activity. The patient must be careful to keep the skin in the area clean and dry to prevent excoriation, especially in the warm weather when there is much perspiration. The device is easily applied and removed by the patient himself and he can take it off any time it becomes uncomfortable.

The process is necessarily slow and the patient must usually wear the device for several weeks before any effect becomes apparent. Some will just not bother with it, but there is no question but that the continued traction can draw the testis down farther. See figure 3.

The advantage of this method is that the tension may be continued indefinitely and in increasing amounts if desired, time not being limited by the period during which one or more sutures will cut through the tissues. Of course, traction is not started until the anastomosis between the testis and thigh is well healed so that separation of the anastomosis will not occur.

When the testis has either reached a desired position or it is felt that no further improvement is to be expected with reasonable amounts of tension, a trial period without tension will then indicate whether retraction is going to occur.

In a couple of cases, an attempt was made to provide a point for traction by making a button hole through the tissue of the gubernaculum or of the reflected tunica vaginalis. A skin tunnel was then made through this opening by making two small scrotal incisions and sewing them together through the loop. It was possible to get some traction on the testis by this method, but in neither case was the attempt clinically successful. In one case the skin bridge was too small and the tension soon cut through, even with a small strip of flat rubber tissue to exert pressure. In the other, the patient did not cooperate. See figures 4 and 5.

The number of cases where such measures are considered is small; the great majority require only temporary suture fixation or gubernacular fixation to the thigh and later detachment.

Our experience with secondary operations to bring down the testis which could not be properly located on the first operation has been small but disappointing. We have come to the conclusion that the first operation is the best time to get whatever mobilization of the testis it is possible to obtain. The second operation has always been attended with much more difficulty from adhesions; anatomical landmarks are lost and the testis has been no more willing to come down on the second operation than it was on the first.

Despite Bevan's confident assertion that the spermatic vessels could be divided

without serious consequence, the experience of many urologists has been contrary and atrophy of the testis has been the eventual result.

There will occasionally arise the question as to whether orchiectomy should be done. Despite every effort there are some cases in which the testis cannot be brought down far enough to be placed in the scrotum at all, much less to be fastened to the thigh. Also, some of these testes will be very hypoplastic. The answer to the question as to whether a testis should be removed will depend on three factors: 1) the site to which it is possible to bring the testis; 2) the apparent worth of the testis from a functional standpoint; and 3) the state of the other testis.

If the testis on the opposite side is apparently normal, it would be poor policy to leave a hypoplastic testis in the groin or in the abdomen. If the involved testis is of nearly normal size, one would be more reluctant to sacrifice it even though the other testis were normal. It is a debatable point whether such a testis might best be left in the region of the external ring outside of the fascia but not immediately over the pubic bone. In such a position it would be amenable to regular examination and any change in its size would be readily apparent. With a normal testis on the other side, one should never replace a cryptorchid testis in the abdomen or leave it in the inguinal canal. The possibility of malignant degeneration outweighs the expected benefit from such a procedure.

Where the testis on the other side is subnormal or of unknown value, one will naturally extend his efforts to preserve even a hypoplastic testis. Even so, one should hesitate to replace such a testis in the abdomen, preferring to leave it in the subcutaneous inguinal space where it would be amenable to examination. The excellent results of replacement androgen therapy makes one less hesitant to remove an abnormal testis but, where one can do so without extraordinary risk, one should leave the patient with a functioning testis so he will not have to rely on constant replacement medication.

SUMMARY

Surgery is the accepted treatment for cryptorchidism which does not respond to a trial of endocrine therapy.

The basic principle of surgical treatment is complete freeing of the cord structures from all adhesion to adjacent structures.

Fixation of the testis in the scrotum is desirable and necessary in nearly all instances to insure against retraction from the scrotum.

It is occasionally possible to continue traction indefinitely after surgery by use of an elastic band.

Orchiectomy is only rarely indicated.

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DISCUSSION

DR. RICHARD CHUTE (Boston, Mass.): At what age should the surgery be performed?

DR. ARCHIE L. DEAN (New York, N. Y.): In outlining a procedure for the treatment of cryptorchidism, four fundamental postulates must be considered: 1) Any undescended testis may become cancerous. Probably the incidence is more than 10 per cent. 2) Placing the testis in the scrotum after puberty does not prevent subsequent cancer formation. Possibly orchiopexy even in infancy is not an absolute safeguard. 3) All undescended testes are accompanied by a hernia. Since it is not known how early in life malignant degeneration may occur in these testes nor when sterility will be established and since these infants should have their hernias repaired anyway, it appears to me that orchiopexy together with hernia repair is best performed before the age of two years in otherwise healthy infants. While statistical studies are now inadequate to show precisely the benefits of such a procedure, it is likely that each testis so treated will be given every opportunity for normal development in its most favorable environment.

DR. JOSEPH H. KIEFER: We believe a good age for surgery is seven or eight. However we take them when we can get them, even though it is late and past puberty.

We have had tumors in testes which have been brought down, as I know you all have. The bringing down does not reduce the incidence of malignant degeneration but if it does occur, it is immediately apparent. Otherwise with the testis in the abdomen, the diagnosis cannot be made until too late.

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